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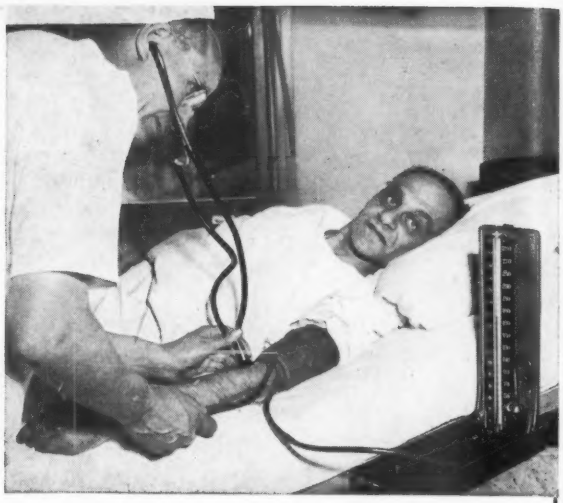

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1952

ORIGINAL ARTICLES

CLINICAL USE OF CATION EXCHANGE RESINS IN THE TREATMENT OF CONGESTIVE HEART FAILURE*

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SODIUM plays a central role in the fluid retention of congestive heart failure. Consequently, restriction of its intake is an important feature in treatment. Dietary curbs must often be severe, however, to be effective, and this may be difficult and occasionally too expensive for the patient. Because of such considerations and on the basis of animal experiments, Dock[7] in 1946 suggested the use of cation exchange resins to decrease absorption of dietary sodium from the gastrointestinal tract. The initial clinical trials were carried out by Greenblatt *et al.*[10], Cobbey *et al.*[4], and Irwin *et al.*[13]. The exchange substances were shown to be effective in increasing the stool content of sodium, and therefore of use in the treatment of congestive heart failure. Greenblatt's group showed that they could be given on a long-term basis without untoward effects. A number of preliminary reports appeared in 1950[5,6,14,16] confirming the usefulness of these resins, but emphasized the occasional appearance of serious toxic effects. Shortly afterward, Dock and Frank[8] reviewed the status of resin therapy and concluded that it was useful in limiting the absorption of sodium and producing weight loss in cardiac, cirrhotic, and nephrotic patients. They noted its value both in potentiating mercurial diuresis and in patients sensitive or refractory to such diuretics. However, the authors emphasized that ion exchangers were still in an experimental stage and that careful clinical and laboratory follow-up was necessary if they were to be used safely. A number of clinical studies[2,12,15,17,20] have appeared since then with conclusions which have, in general, corroborated the above findings. In a recent review, McChesney, Dock, and Tainter[18] em-

* Supported by a grant from the Massachusetts Heart Association.

phasized that results of animal experiments justified long-term studies in humans.

There have been a number of detailed discussions on the composition of resins and the theory of ion exchange[1,3,19]. The resin used in the first portion of this study* was a cross-linked polyacrylic (carboxylic) resin. Potassium comprised 22% and ammonium 78% of the exchange ion.† This resin in the usual daily dose of 45 grams supplies the patient with 60 mEq. of potassium daily.

The second portion of the study reports the results of treatment with an ammonium cycle sulfonic resin[16].

Our purpose in the present study was to evaluate the effect of prolonged administration of a cation exchange resin used as an adjunct in the management of patients with congestive heart failure. Only out-patients were chosen for treatment with the carboxylic resin since it was felt that a more useful estimate could be made with the patient in his accustomed environment. Both hospitalized and out-patients were treated with the ammonium sulfonic resin.

Ammonium–Potassium Carboxylic Resin†

Procedure. Twenty-two patients were selected who had congestive heart failure of sufficient severity to require mercurial injections at intervals of 2 to 7 days, digitalis, and low salt diets. Ammonium chloride was used in 16 cases. Ten of the group had been hospitalized one or more times because of heart failure during the year prior to initiation of the study. Duration of symptoms ranged from 1 to 30 years with an average of 10.5 years. Other pertinent data are presented in Table 1.

At the initial visit a complete history and physical examination were done. Additional studies included an electrocardiogram, chest roentgenogram, serum sodium and potassium, vital capacity, hemoglobin, urinalysis, and when indicated, a serum nonprotein nitrogen. Each patient was followed at least 2 weeks prior to resin therapy to evaluate his therapeutic requirements. The patient was then started on the exchange resin in a dose of 15 gm. 3 times daily at meal time in coffee, tea, water, fruit juice, or ginger ale. Weekly clinical follow-up visits were made with less frequent determinations of serum sodium, potassium, calcium, and electrocardiogram. Serum sodium and potassium were determined by the method of Hald[11], using an internal standard flame photometer and serum calcium by the method of Fiske and Adams[9].

With the onset of resin therapy, patients were permitted diets estimated to contain approximately 4.0 gm. of sodium chloride daily and ammonium chloride was discontinued. Further need for mercurial diuretics was determined by the individual's subsequent response.

Results. Duration of Treatment. Seven of the 22 patients were maintained continuously on the resin for 5 to 38 weeks. Of the 7, one failed to return after 5 weeks and another died of acute myocardial infarction during the fifth week. The remaining 5 patients were followed 26 to 38 weeks. Resin was discontinued in 15 patients after 1 day to 12 weeks of treatment because of toxic reactions in 11 patients and insufficient response in 4 patients. Therapy was reinstituted in 7 of this group with 3 of these maintained 1 to 10 weeks. Resin was withdrawn a second time because of a toxic reaction in the other 4 patients with a subsequent successful third trial in 2 of the latter. Thus, 12 patients ultimately were successfully treated with this resin.

Clinical Status. Three patients showed improvement including decreased peripheral edema and loss of weight during therapy. Nine additional

* A preliminary report of this portion of the present study was presented by title before the meeting of the American Heart Association, June, 1951.

† This resin under the name of Resodec^{R} was generously supplied by Smith, Kline & French, Inc., Philadelphia, Pennsylvania.

patients showed no significant change in congestive heart failure. However, they were eating more liberal sodium diets and requiring decreased amounts of other medications. Ten patients became worse as indicated by increased peripheral edema, weight gain, and increase in dyspnea while taking the resin. In 2, this was related to the appearance of respiratory infections, and resin treatment was discontinued in both. Subsequently, resin was successfully reinstituted in one of these patients. In 5 patients increased congestive heart failure occurred simultaneously with toxic effects of the resin gastrointestinal symptoms in 3, digitalis toxicity in 1, and acidosis in the last. Resin was stopped in each of these 5 patients but was reinstituted successfully at a later date in the patient who had digitalis toxicity. There was no obvious cause for resin failure in the remaining 3 patients, and resin therapy was terminated in all. The effectiveness of therapy was not related to the type of heart disease present, age of the patient, or the initial severity of heart failure.

TABLE 1.—THE DIAGNOSIS AND EFFECT ON MERCURIAL REQUIREMENTS OF 22 PATIENTS TREATED WITH CARBOXYLIC RESIN

Patient	*Age*	*Sex*	*Diagnosis**	Rate of Mercurial Injections	
				Before Resin	*During Resin*
1	74	M	ASHD	Every 7 days	None
2	63	M	HCVD	" 5 "	"
3	36	M	RHD	" 2 "	"
4	51	F	HCVD	" 7 "	"
5	50	F	RHD	" 4 "	Every 5 weeks
6	65	F	RHD	" 2 "	" 9 days
7	49	F	RHD	" 2 "	" 2 "
8	51	F	HCVD	" 2–4 "	" 7 "
9	53	F	HCVD, ASHD	" 7 "	" 5 weeks
10	60	M	RHD	" 3 "	None
11	66	M	ASHD	" 7 "	"
12	47	F	RHD	" 2 "	Every 7 days
13	46	F	RHD	" 7 "	" 5 weeks
14	47	M	RHD	" 2–3 "	" 3 days
15	68	M	ASHD	" 7 "	None
16	34	F	RHD	" 3 "	" 7 days
17	48	F	RHD	" 7 "	None
18	58	M	ASHD	" 7 "	"
19	58	F	RHD	" 7 "	"
20	49	F	RHD	" 7 "	Every 3–4 weeks
21	64	M	ASHD	" 2–3 "	" 5 days
22	46	M	RHD	" 4–7 "	" 10 "

All patients were maintained on digitalis and low salt diets before resin therapy.

* ASHD—Arteriosclerotic heart disease.
HCVD—Hypertensive cardiovascular disease.
RHD—Rheumatic heart disease.

TOXICITY. *Gastrointestinal.* Twenty patients complained of one or more symptoms referable to the gastrointestinal tract. The frequency of various symptoms is outlined in Table 2. Gastrointestinal complaints were associated with other manifestations of digitalis toxicity in 5 of these 20 patients and recurred in 1 case. They appeared simultaneously with increasing congestive heart failure in 4 patients and were seen with acidosis in 1 patient. The local action of resin appears

to have caused the gastrointestinal complaints among the remainder.

It was necessary to discontinue therapy during 9 trials in 7 patients because of gastrointestinal symptoms. In 2 of the 9 trials these symptoms appeared in association with digitalis toxicity, in one they were associated with increasing congestive heart failure, and in one patient with acidosis.

TABLE 2.—THE INCIDENCE OF TOXIC MANIFESTATIONS IN 20 OF 22 PATIENTS TREATED WITH CARBOXYLIC RESIN

Toxicity	*Number*
Gastrointestinal effects	20*
Nausea	11
Anorexia	10
Vomiting	8
Constipation	6
Diarrhea	4
Bleeding hemorrhoids	1
Digitalis effects	8
Clinical acidosis	1
Skin rash	1

* Includes cases of excessive digitalis effect and acidosis manifesting gastrointestinal symptoms.

There was no evident added factor in 5 patients. Treatment was subsequently reinstituted and successfully maintained in the one patient who developed these symptoms in association with increased congestive heart failure, in both associated with digitalis toxicity, and in one of the group where no added factor had been detected. A second trial of therapy was initiated in 2 other patients of this latter group, and both again experienced gastrointestinal symptoms. No further trial of therapy was made in the patient who had associated acidosis.

Symptoms appeared during the initial week of therapy in 13 of the 20 patients and in 17 of the 20 during the first 2 weeks of therapy. All had noted these symptoms by the end of the sixth week of treatment. They recurred later in 2 patients.

Digitalis Toxicity. Eight patients manifested some sign of excessive digitalis effect during treatment (see Table 3), including ventricular premature beats in 3, multiple ventricular premature beats producing bigeminy in 3, and ventricular rates below 60 in the presence of auricular fibrillation in 2 patients. In addition 2 other patients showed increased digitalis effect as evidenced by T wave and S-T segment changes in the electrocardiogram. Resin was omitted in 4 of these patients. In one patient the omission was partially due to intolerance of the resin bulk and in another to concurrent acidosis. Digitalis was discontinued temporarily in 2 of the 4 patients because of severe gastrointestinal symptoms and bigeminy. In both of these cases, resin was subsequently successfully reinstituted along with diminished digitalis dosage.

The toxic effect was eliminated on 3 occasions by decreasing digitalis dosage without changing resin treatment. In one patient a decrease in resin dosage with no change in digitalis schedule reduced toxicity. In one of the patients with only electrocardiographic evidence of excess digitalis effect, no change in treatment was made, and in the other, decreased digitalis dosage led to a return of the electrocardiogram to its pretreatment appearance.

Serum sodium and potassium values were available at the time of digitalis intoxication in 7 of the 8 patients with clinical evidence of such toxicity. There was a decrease in serum potassium of more than 0.5 mEq./L. in 4 of the 7 patients but in no case was this to a level below 3.5 mEq./L. (see Table 3).

Digitalis toxicity appeared within the first week of treatment in 4 of the

10 cases and by the fourth week in all. It reappeared in 3 patients at a later date.

Electrolyte Effects. No consistent changes in serum sodium levels were seen in this series of patients. Seven patients had a decrease of more than 5 mEq./L. and 5 of these were to levels slightly below normal range. Two patients had an increase of more than 5 mEq./L., but both final values were within normal range. No significant change was noted in the remaining patients.

Serum potassium levels in 5 patients decreased more than 0.5 mEq./L. One of these was to a level below 3.5 mEq./L. No significant change occurred in the remaining patients.

No changes in serum calcium values were noted.

Clinical evidence of excessive sodium, potassium, or calcium depletion was not seen. There were no electrocardiographic changes consistent with hypokalemia or hypocalcemia.

One patient exhibited clinical acidosis after 3 weeks with a serum carbon dioxide–combining power of 37 volumes 100 cc. and symptoms of lightheadedness, weakness, drowsiness, and nausea. He was the sole patient in the series with previous evidence of renal damage, as indicated by the presence of white blood cells and many granular casts in the urine sediment and a serum nonprotein nitrogen of 55 mg./100 cc.

Skin Rash. One patient experienced a generalized pruritic maculopapular rash which slowly disappeared when the resin was withdrawn. It reappeared on 2 subsequent occasions with reinstitution of therapy.

TABLE 3.—THE MANIFESTATIONS OF DIGITALIS TOXICITY IN 8 PATIENTS TREATED WITH CARBOXYLIC RESIN, WITH ASSOCIATED ELECTROLYTE FINDINGS

			Serum Levels mEq. L.			
			Control		*During Toxicity*	
Patient	*Symptoms*	*ECG Findings*	*Na*	*K*	*Na*	*K*
2	Anorexia	Ventricular premature beats	143.5	5.25	136.7	3.89
11		Ventricular premature beats	143.0	4.88	137.3	3.84
13		Bradycardia				
14	Nausea, vomiting	Bigeminy*	141.8	4.39	142.5	4.40
15		Bradycardia	134.5	4.35	135.3	4.25
16		Bradycardia, ventricular premature beats	137.0	3.87	136.0	3.84
19	Nausea, vomiting	Bigeminy*	152.8	4.33	145.2	3.59
22	Nausea, vomiting	Bigeminy*	144.5	4.37	139.7	3.66

* Produced by ventricular premature beats.

Ammonium Sulfonic Resin‡

Procedure. An additional 22 patients with chronic congestive heart failure were treated

‡ This resin under the name Win-3000R and CaliradR tablets were generously supplied by Winthrop-Stearns, Inc., New York, New York.

with an ammonium sulfonic resin. All of these patients had been previously digitalized and most required mercurial diuretics every 2 to 7 days. The diagnoses in this group were rheumatic heart disease in 13, arteriosclerotic heart disease in 5, hypertensive heart disease in 1, coarctation of the aorta in 1, cor pulmonale in 1, and combined hypertensive and arteriosclerotic heart disease in 1 patient. Fifteen of these patients were treated in the hospital and 7 as outpatients.

The initial daily dose of resin was 60 gm. divided into 3 equal parts taken after meals. Subsequent dosage varied with response. It was accordingly altered in 8 patients, and ultimate maintenance dosage ranged from 28 to 96 gm. While taking resin they received diets containing approximately 6 gm. of sodium chloride and were continued on their usual dose of digitalis. Additional diuretics were given as indicated by the patient's clinical status.

Results. DURATION OF TREATMENT. The 15 hospitalized patients were treated from 1 to 3 weeks, and the 7 out-patients were followed from 3 to 21 weeks on continuous resin therapy.

CLINICAL EFFECT. Since 15 of these patients were hospitalized during treatment, it was possible to follow their response to resin therapy more closely than in the previous out-patient series. The usual response was diuresis beginning on the second day of therapy, and associated with this, a weight loss of 1 to 2 lb. daily until a stabilized weight level was reached. Total weight loss varied from patient to patient and was related to the degree of fluid retention. The usual maintenance dose of resin failed to prevent increased severity of heart failure in 3 patients when infection of the upper respiratory tract or reactivation of rheumatic carditis occurred. Of 6 patients refractory to mercurial diuretics, 2 responded to resin. There were no patients responsive to mercurials who were refractory to resin. In addition, 4 patients who developed hypocalcemia were not maintained by the resin when added calcium was given. A few patients felt that any benefit from the resin was counteracted by its inconvenience, and they preferred a mercurial low salt regimen.

Toxicity. *Gastrointestinal.* Constipation was noted in 5, mild anorexia in 2, nausea and vomiting in 4 patients. The nausea and vomiting in 3 of these 4 was felt to be associated with digitalis toxicity.

Digitalis Intoxication. Three patients developed nausea, vomiting, and bigeminy which disappeared with omission of digitalis, although resin was continued. In 2 of the 3 patients these symptoms appeared at a time when serum potassium levels had fallen below 3.0 mEq./L. Potassium levels were not available in the third patient.

Electrolyte Changes. Serum sodium levels were determined in 14 patients, and there was no significant alteration in 13. In one patient who received a rice diet simultaneously with resin, a low salt syndrome was produced.

Serum potassium levels declined significantly in all 13 patients in whom it was determined. This frequently occurred during the first week. Levels below 3.0 mEq./L. were noted in 4 patients, although none showed clinical or electrocardiographic evidence of hypokalemia.

Depression of calcium levels was generally present by the end of the first week, and 6 patients had levels as low as 7.5 mg./100 cc. after the second week. None showed the signs, symptoms, or electrocardiographic changes of hypocalcemia. Four patients were given supplementary calcium tablets* with subsequent return of serum levels to normal. In each of these cases edema reaccumulated and low serum potassium levels rose strikingly toward normal. It seems likely that, during added calcium therapy,

* Calirad.

more of the resin was saturated with calcium, resulting in increased intestinal absorption of sodium and potassium.

Acidosis was noted within 2 weeks in the 15 patients having plasma carbon dioxide–combining power determination (30 to 35 volumes/100 cc.). Plasma chloride values rose consistently during this same period with values encountered up to 120 mEq./L.

Discussion. The present study reaffirms the value of an ammonium–potassium cycle carboxylic resin in the treatment of congestive heart failure. The symptoms and signs of heart failure remained unchanged or improved in 12 of 22 patients during its administration. This was achieved in the presence of a more liberal sodium intake and, in many instances, a marked decrease in mercurial diuretic requirements. Most of the patients maintained on resin preferred it to a low salt–mercurial regimen. The ammonium sulfonic resin was also effective in the treatment of heart failure, but the high incidence of serious toxic effects limits its clinical usefulness.

The occurrence of respiratory infection, active carditis, or a toxic effect of the resin has been associated in some patients with failure of the resin. In these cases it has been necessary either to increase the dose or to revert to a mercurial–low salt regimen.

Careful clinical follow-up is necessary if therapy is to be successful and the possibility of serious untoward effects are to be minimized. This is particularly true during the first 6 weeks, at which time most of the toxic effects will make their appearance. All the toxic effects that occurred with the carboxylic resin used in this study were manifest clinically with the exception of minor electrocardiographic changes. Consequently, we do not feel that elaborate laboratory studies are necessary to follow these patients.

Complications of Therapy. Gastrointestinal complaints have been a major limiting factor in the use of cation exchange resins. Not uncommonly they are severe enough to terminate therapy. The carboxylic resin used in this study has shown a high incidence of such toxicity, requiring cessation of therapy in 7 of the patients. Gastrointestinal symptoms were somewhat less common in the group treated with the sulfonic resin.

Digitalis toxicity also occurred frequently in this series. It has been suggested by Kraus[16] and Hay and Wood[12] that the appearance of digitalis toxicity might be associated with production of hypokalemia by the resin. In the present group treated with ammonium sulfonic resin, the manifestations of digitalis intoxication were noted in 2 patients when the serum potassium levels were below 3.0 mEq./L. However, in the carboxylic resin group no consistent alterations of serum electrolyte concentrations were seen in 7 patients in whom determinations were available when clinical signs of such toxicity were present. The explanation for the common occurrence of excessive digitalis effect remains obscure. It must be remembered, however, that serum potassium values may not accurately reflect the potassium concentration in the heart muscle.

The third reported major complication of resin therapy has been the production of serum electrolyte abnormalities. Occurrence of hypokalemia was first noted by Irwin *et al.*[13]. Four studies reported before the Society for Clinical Investigation in 1950[5,6,14,16] also noted evidence of potassium loss in patients. In addition, 2 of these[14,16] noted the production of hypocalcemia. Kahn and Emerson[14] suggested the use of a carboxylic resin in a combination

of ammonium and potassium cycles to avoid these toxic effects. In the present study this type of resin has been used up to 38 weeks without causing significant lowering of serum electrolytes. It is of interest that serum calcium fell to 7.5 mg./100 cc. in one patient during treatment with ammonium sulfonic resin, whereas no fall was noted in a subsequent trial in this patient after 33 continuous weeks of carboxylic resin therapy.

Compensated acidosis occurs not uncommonly with all cation exchangers, but is partially reduced by the inclusion of potassium in the exchange position. Renal impairment, with reduced capacity for ammonium production, seriously predisposes to uncompensated acidosis. Hyperkalemia may occur if the ammonium–potassium form of the resin is used when the kidney's ability to excrete potassium is diminished.

Recommendations for Use. Pre-Treatment Evaluation. It should be remembered that these materials can accomplish no more than does the rigid restriction of sodium intake. A careful search should be made for both impairment of renal function and previous digitalis toxicity. A baseline electrocardiogram is useful if the question of digitalis intoxication or electrolyte abnormality arises later. Determinations of serum sodium, potassium, and calcium are desirable but not necessary.

Dosage. Empirically, an inital dose of 15 gm. 3 times daily has been found satisfactory. It is subject to change at any time in the presence of insufficient response or toxicity. Any appealing beverage, with the exception of milk, is a suitable vehicle.

Follow-up. Each patient should be seen weekly for the first 6 weeks. Subsequently, visits may be less frequent. The presence of gastrointestinal complaints may indicate local irritation caused by the resin, digitalis intoxication, or acidosis. Pulse changes are helpful in detecting excessive digitalis effect and usually parallel electrocardiographic changes. Constipation or increased stool frequency may be counteracted by simple means. Symptoms suggestive of electrolyte abnormality may require further laboratory investigation.

Other Treatment. Most of our patients have been maintained on an unlimited diet with no added salt. Administration of ammonium chloride should be discontinued since the resin supplies the equivalent of a usual daily dose. Digitalis should be continued but the dosage may have to be altered if toxic signs appear. Mercurial diuretics are adjusted to the new requirements, which are frequently diminished.

Conclusions. Twenty-two patients with congestive heart failure were treated with an ammonium–potassium carboxylic resin for periods ranging from 1 day to 38 weeks. Regular diets without added salt were instituted, ammonium chloride was discontinued, and mercurial administration was decreased when treatment was initiated. Twelve patients were successfully treated with the resin. In 3 of these, the cardiac status improved, and 9 were maintained unchanged but with a liberalized salt intake and less diuretic medication. In 10 patients congestive symptoms increased, concomitantly with an acute respiratory infection in 2, with toxic effects of the resin in 5, and for no obvious reason in 3. Gastrointestinal symptoms were the most common toxic manifestations, occurring to some degree in 20 patients, and necessitating termination of resin therapy in 7. Evidence of excess digitalis effect was noted 8 times. Acidosis and toxic skin rash also were observed.

This type of resin appears to be comparatively safe for general clinical use provided patients are followed regularly and carefully, and it was an effective and practical form of therapy in about half of the cases studied.

Twenty-two additional patients were treated with ammonium sulfonic resin for periods ranging from 1 to 21 weeks. Other treatment was modified in the same manner as described for the carboxylic resin group. Seven patients did not improve with resin administration. In addition, supplementary calcium therapy in 4 patients who developed hypocalcemia produced a loss of effectiveness of the resin. Hypocalcemia and hypokalemia were the most common toxic effects and limit the practical usefulness of this resin. Gastrointestinal symptoms and digitalis toxicity were also seen.

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THE EFFECT OF ANTABUSE ON THE ELECTROENCEPHALOGRAM*

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The therapeutic use of Antabuse, tetraethylthiuramdisulfide, to prevent chronic alcoholics from being able to tolerate alcohol is becoming more widespread. Its therapeutic value is not within the scope of this paper but has been reported by one of the authors and other investigators[2,4,10]. The drug was first used in the Scandinavian countries and much of the pharmacological work with it has been done there. A person who has been on an adequate dose of Antabuse and then ingests alcohol suddenly develops a number of very unpleasant symptoms: severe flushing of the face, tachycardia, dyspnea, dizziness, and frequently nausea and vomiting. The blood pressure falls alarmingly and the patient experiences varying degrees of vascular collapse. This unpleasant reaction is the basis of its therapeutic value. The knowledge that an unpleasant reaction will be precipitated by ingestion of alcohol prevents the patient from reverting to his old habits. The odor of acetaldehyde may be noted on the breath of patients receiving Antabuse and blood levels of acetaldehyde are found to be high. Studies by Graham[7], Kjeldgaard[8] and others indicated that acetaldehyde, one of the usual oxidation products of ethyl alcohol, can no longer be oxidized further in the liver by the aldehyde oxidase enzymes and, therefore, accumulates, producing toxic symptoms. Chemically the Antabuse molecule contains 2 sulfur atoms linked so as to be capable of acting as strong hydrogen acceptors. The affinity of the liver aldehyde oxidase protein for the Antabuse molecule is 350 times its affinity for acetaldehyde[7]. Christensen[3] has indicated there is more to the Antabuse–alcohol reaction than the mere production of high blood acetaldehyde levels, but this does explain many of the toxic signs and symptoms.

It would be expected, then, that Antabuse, because of its affinity for enzymes, might have certain toxic properties itself, quite apart from the toxicity of the products of Antabuse–alcohol reaction. Clinically this appears to be true. Gastrointestinal disturbances, lethargy, somnolence, and decreased mental acuity are frequently seen and can often be reduced or eliminated by lowering the Antabuse

* Antabuse furnished for research purposes by Ayerst, McKenna and Harrison, Ltd.

dosage. Bennett and associates[1] reported severe psychotic reactions in 4 patients within 3 weeks after being put on Antabuse. The symptoms suggested a toxic delirium in each, and promptly cleared on discontinuation of Antabuse. There was evidence of organic brain disease in these patients before onset of Antabuse treatment. Recently 2 other reports on psychotic reactions during Antabuse medication have appeared in the literature[6,9].

Experimental studies have confirmed the toxicity of Antabuse. Edwards[5], measuring oxygen uptake of liver tissue by the Warburg technique, demonstrated an inhibition of about 85% when Antabuse in relatively high concentrations was present. He suggested that the cyanide or cyanate group contained in the thiuram nucleus of the Antabuse molecule was released. Thus a histotoxic anoxia may be produced by Antabuse. However, as far as we know this possibility has not been confirmed experimentally as a process occurring in subjects receiving Antabuse. Interestingly, cyanamide produces a hypersensitivity to alcohol similar to Antabuse. Child and associates[2], administering toxic doses of Antabuse to experimental animals, showed marked histological changes in the kidney, liver and brain. The latter showed a patchy demyelinization similar to the lesions of multiple sclerosis.

Objective and Procedure. Because of its apparent histotoxic properties it seems reasonable to speculate that alterations in metabolic processes would be reflected in the electroencephalogram. Our clinical studies with Antabuse have included routine electroencephalograms before and during Antabuse medication. Clinical workup included also laboratory studies on liver and kidney function, physical and neurological examination, psychiatric evaluation, and often psychological testing. Our electroencephalograms were recorded on a standard Grass 8-channel machine, using both monopolar and bipolar recordings. Routine records were approximately 20 minutes in duration, including 3 minutes of hyperventilation. Sleep records were not obtained in all patients and the sleep evaluations were not included in this report. The Gibbs and Lennox system of electroencephalogram classification was used, except that we further subdivided the classification of slow and fast records. These records were divided into mild, moderate and severe degrees of dysrhythmia and were designated, for example, as S-1 Mild, S-1 Moderate and S-2. A questionable normal record was employed as a means of designating those records, often poorly organized, which, although composed predominantly of frequencies with normal limits, also contain scattered slow and fast waves. Thirty patients were employed in this study. With 2 exceptions the patients were on Antabuse at least 2 weeks and some up to 7 months. Doses ranged from 0.25 to 0.75 gm. per day, being 0.5 gm. in 24 of the 30 patients. In order to facilitate the understanding of the change observed in the electroencephalograms of patients on Antabuse we have arranged our patients in 3 groups in terms of the initial or pre-Antabuse electroencephalogram. Group 1 was composed of patients with normal electroencephalograms. Group 2 included those individuals with questionably normal brain waves and Group 3 consisted of persons with dysrhythmic pre-Antabuse records.

Results. Group 1 consisted of 15 individuals with normal pre-Antabuse electroencephalograms. Five of this group had pre-Antabuse records in which the dominant frequency was within the 8 to 12 cps (cycles per second) range. Four of these remained unchanged on Antabuse and 1 became an S-1 moderate with a questionable focal slowing. This same individual 1½ months after discontinuation of treatment still had a mildly slowed record with asymmetry. Ten of this normal pre-Antabuse group of 15 were classified as having predominately low-voltage fast records (LVF). Eight remained normal on Antabuse, 2 changed slightly showing diffuse slowing and were classified as S-1 Mild. Both of these S-1 Mild records showed a marked increase in the response to hyperventilation. Of the 8 records re-

maining normal in this group of LVF records, 6 showed moderate to marked increase in the resting alpha amplitudes.

Group 2 consisted of 9 individuals with questionable normal pre-Antabuse records. In 4 of these, the dominant frequency was within the 8 to 12 cps range. Antabuse increased the slowing in all 4. One became S-1 Mild, one an S-1 Moderate, one an S-1 Moderate with questionable focal slowing, and one a clear S-2 (Fig. 1). Five patients in this borderline pre-Antabuse group of 9 individuals were classified as having questionable normal low-voltage fast (LVF) records pre-Antabuse. All 5 also became more disturbed. Three became S-1 Mild and one of these showed a borderline paroxysmal slowing in response to hyperventilation. One became an S-1 Moderate and another an F-1 Mild. In all 5 a marked increase in the amplitude of the alpha activity was seen.

Group 3 consisted of 6 individuals who started with dysrhythmic pre-Antabuse records. One, an S-1 Mild, became an S-1 Moderate; another, an F-1 Mild, became an F-2 and S-1 Moderate with high amplitude, fast and slow activity and poor organization. Two F-1 Moderates showed, on Antabuse, the addition of slow activity with the preservation of the fast. One of these became an F-1 Moderate with focal asymmetry and with the addition of focal slowing, and the other became an F-1 Moderate and S-1 Mild (Fig. 2). One record showing a mixture of fast and slow activity pre-Antabuse demonstrated a marked increase in slow activity and the appearance of paroxysmal slowing with hyperventilation; and lastly, one record showing a focal slowing before Antabuse demon-

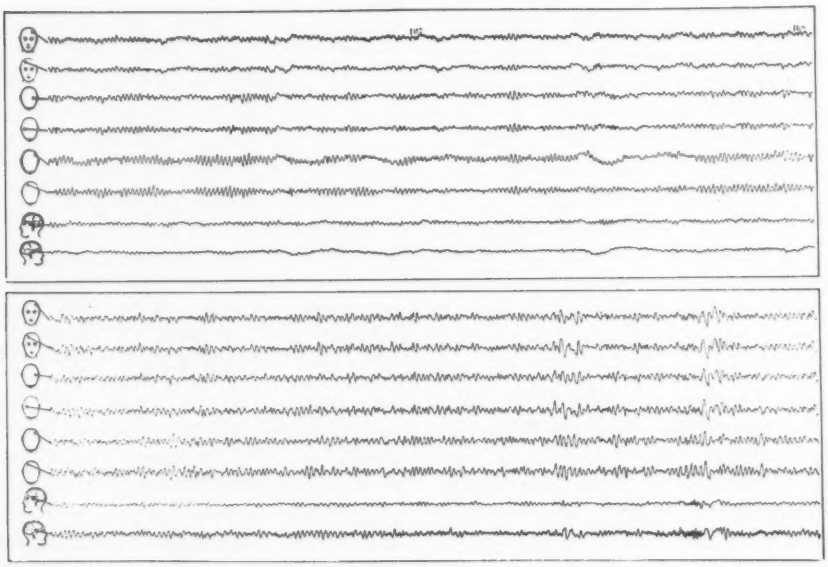

FIG. 1.—Conversion of questionable normal electroencephalogram (above) to a frankly abnormal tracing (below) during Antabuse therapy (0.5 gm. daily for 7 weeks) in a 46-year old male. S-2 Classification after treatment. (See text for explanation of classification.)

strated a marked accentuation of the S-2 focus with the addition of a paroxysmal slow response to hyperventilation while on Antabuse.

The percentage of questionable normal and clearly dysrhythmic pre-Antabuse electroencephalograms is considerably higher than that found in

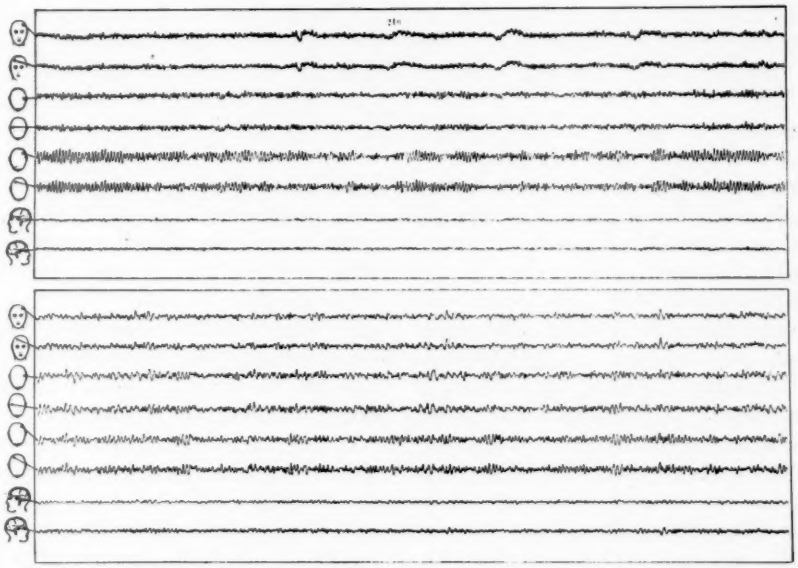

FIG. 2.—(Below) Additional changes induced by Antabuse therapy (0.5 gm. daily for 4 weeks) in a 49-year old male with an abnormal pre-therapy electroencephalogram (above). Classification before treatment was F-1 Moderate; after treatment, F-1 Moderate and S-1 Mild. Note poor organization after treatment. (See text for explanation of classification.)

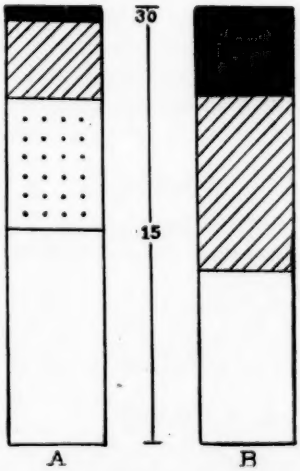

FIG. 3.—Summary of EEG findings in 30 patients (A) before and (B) during Antabuse therapy. Normal EEG, white area; questionable normal, stippled area; mild or moderate disturbances, cross-hatched area; severe dysrhythmias, black area.

our normal control series. This finding suggests that chronic alcoholics have a high percentage of disturbed brain waves. However, we feel that this aspect of the problem requires further investigation and does not detract from our finding that Antabuse has a definite effect upon cortical activity (Fig. 3).

Summary. A series of 30 patients was studied who had been placed on Antabuse as a therapeutic measure for alcoholism. Those persons with normal brain waves pre-Antabuse had normal records while on Antabuse in 12 out of 15 instances (80%), and what disturbances did appear were not severe. Patients whose electroencephalograms were classified as being questionably normal prior to Antabuse had records which became distinctly dysrhythmic in all cases after a period on Antabuse therapy, while records that were clearly disturbed before Antabuse invariably showed proportionately the greatest increase in abnormalities on the drug. The amplitude of the dominant frequency tended to increase and low voltage fast records often showed the appearance of higher amplitude frequencies within the alpha range. The effect of hyperventilation in the questionable normal and disturbed records frequently became much more pronounced on Antabuse, often with a paroxysmal response. In addition our findings suggest that hidden foci became apparent and that already recognizable foci became more prominent on Antabuse.

Conclusions. 1. Antabuse, when employed in therapeutic doses, produces definite toxic symptoms and in addition exerts a toxic influence upon the brain as demonstrated by alterations in the electroencephalogram.

2. These findings support the belief that Antabuse may produce a histotoxic anoxia secondary to interference with respiratory enzyme activity in cortical cells.

3. The electrical changes of the cortex resulting from Antabuse are usually seen as an increase in the amplitude and a slowing of the cortical rhythm.

4. The degree of change seen in the electroencephalogram is influenced by the stability of the cortex prior to Antabuse medication. Normal brain waves are apt to remain normal (in our series only 20% showed a disturbance on Antabuse) but 100% of the initially dysrhythmic tracings become more disturbed.

5. Because of the toxic effects of Antabuse upon the brain the drug should be used with caution in patients suspected of organic brain disease and particularly in patients with a history of a convulsive disorder.

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EFFORT SYNCOPE AS AN EARLY MANIFESTATION OF PRIMARY PULMONARY HYPERTENSION

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In a comprehensive study of pulmonary artery disease Brenner[4] noted the following clinical features as diagnostic of primary pulmonary arteriosclerosis: 1) Severe cyanosis with edema and comparatively little dyspnea; 2) clinical and electrocardiographic evidence of hypertrophy of the right ventricle but not of the left; 3) An accentuated second pulmonary sound perhaps with a pulmonary diastolic murmur, but without murmurs indicative of valvular or congenital heart disease; 4) no clinical or roentgenographic evidence of chronic pulmonary disease; 5) roentgenographic evidence of enlargement of the right side of the heart with prominence of the pulmonary artery and conus of the right ventricle but with normal shadow of the left auricle; 6) no evidence of syphilis. Although syncopal attacks were a striking feature in one of the cases observed by Brenner, syncope was not listed as an essential diagnostic sign of primary pulmonary arteriosclerosis. It is the purpose of this report to show evidence that effort syncope may be an early manifestation of this disease and represents then a sign of outstanding diagnostic importance.

Right ventricular hypertrophy, not accounted for by chronic pulmonary or heart disease, is a prominent feature of primary pulmonary arteriosclerosis. Various investigators have questioned the role of pulmonary arteriosclerosis in the production of hypertrophy of the right ventricle[2,4,6,8,12,15]. According to Brenner, in unselected autopsy cases arteriosclerosis in the pulmonary arteries is no less common than in systemic arteries. It is almost constantly present in the small pulmonary muscular arteries and arterioles in individuals over the age of 40, in the absence of factors believed to raise the pulmonary arterial pressure, and it is common under the age of 40. Brenner pointed out that in some of the reported cases of primary pulmonary arteriosclerosis the vascular changes were less pronounced than in unselected autopsy cases not presenting right ventricular hypertrophy or circulatory symptoms. Brenner[4] therefore concluded "that the vascular lesions are rarely extensive enough in themselves to embarrass the pulmonary circulation seriously and that more probably they and the hypertrophy of the right side of the heart are manifestations of some common unknown cause."

Postmortem findings of marked right ventricular hypertrophy not accounted for by known causes were reported in some cases where pulmonary arteriosclerosis was trivial. The conditions were termed "idiopathic right ventricular hypertrophy"[6] or "right ventricular hypertrophy of obscure origin"[18]. Other cases with similar features were reported as "pulmonary hypertension"[8,12]. In these cases the pressure in the pulmonary circulation was not determined by cardiac catheterization.

However, in a case observed by Wittenberg[20], the presence of marked pulmonary hypertension was demonstrated by physiological studies; postmortem study revealed only trivial arteriosclerosis of the pulmonary arteries. Moschkovitz[15] expressed the view that arteriosclerosis of the pulmonary arteries is nearly always secondary to pulmonary hypertension. In a case of pulmonary arteriosclerosis with right ventricular failure Barrett and Cole[2] observed that the changes found in the pulmonary arteries resembled those of systemic hypertension. The authors concluded that the vascular changes in the lesser circulation were an effect of malignant hypertension. Although the possibility cannot be denied that widespread obstructive structual disease of the pulmonary arteries may increase the resistance in the pulmonary arteries, the available evidence favors the view that the "unknown cause"[4] of both pulmonary arteriosclerosis and right ventricular hypertrophy is primary hypertension in the lesser circulation.

Cyanosis has long been considered an outstanding feature of pulmonary arteriosclerosis[10,21], and patients sufferring from this condition were referred to as cardiac negroes[1]. However, cases have been reported in which cyanosis was mild or absent[4]. Our own experience leads us to believe that severe cyanosis is a late feature of pulmonary hypertension and arteriosclerosis, which may not appear until congestive failure has set in and is therefore of little aid in the early recognition of pulmonary vascular disease. In occasional instances nervous manifestations were reported such as headache, blurred vision, somnolence, vertigo, and syncope[4,6]. The diagnostic significance of nervous manifestations has not been sufficiently appreciated. Unlike cyanosis, syncopal attacks occur sometimes in early phases of pulmonary hypertension and may be the first symptom that causes the patient to seek medical advice; it may even precede the manifestations of right ventricular hypertrophy and dilatation of the pulmonary artery. Syncope figured as a leading diagnostic feature in 3 cases of our observation, and in 6 cases collected from the literature[4,6,11,13,16,20]. A summary of these cases is presented in this report.

Case Reports. CASE 1. G. E., a 31-year old housewife, was admitted to the hospital on February 27, 1927. As a child she had measles and scarlet fever. There was no history of rheumatic fever. At the age of 20 the patient had severe grip. She went through 2 pregnancies; the first, at the age of 26, ended in miscarriage; the 2nd, which occurred 1 year later, was carried to term. Prior to the pregnancies the patient had been shortwinded for some years in association with such efforts as mountain climbing. Shortness of breath increased in 1923, 3 months after successful termination of the second pregnancy. Exercise and particularly brisk movement caused palpitation and a feeling of oppression in the chest. Sometimes, when the patient ran, she lost consciousness. On 2 occasions the patient nearly fainted and complained of rapid pounding of the heart when she briskly got out of bed. Her condition got worse 18 months prior to admission. Climbing a few stairs or carrying a parcel were somtimes followed by syncope. The patient's face became blue and her lips pale, and she lost consciousness. Such attacks were usually followed by vomiting. Three months prior to admission she fainted while walking slowly on the street. As a rule she felt the approach of a syncopal attack. Once, in falling, she struck her head against the pavement, but she never bit her tongue. Seven months before admission swelling of the legs occurred, and later an increase in the size of the abdomen was noted.

Physical Examination. Moderate cyanosis was present. The legs showed edema. The cervical veins were not distended. Numerous râles were heard over the pulmonary bases. The apex beat of the heart was palpable in the 4th intercostal space in the left midclavicular line. A heaving systolic pulsation was noted in the precordial region close to the

lower half of the sternum. The 1st heart sound was palpable in the apical region, and both sounds could be felt in the pulmonary area. Percussion revealed marked dullness over the lower 3rd of the sternum, and in the 2nd and 3rd intercostal spaces in the area of the pulmonary artery and conus. The sternal dullness extended to the right side for a distance of nearly 3 inches. A snapping 1st sound was heard in the apical area. The 2nd pulmonary sound was accentuated and split. No murmurs were heard. The heart rate was 102/min. The radial pulse was regular and of low amplitude. The blood pressure was 115/80. The liver extended 2 fingerbreadths below the costal margin. The spleen was not palpable.

Laboratory Findings. Fluoroscopy revealed marked enlargement of the right ventricle and atrium. There was no dilatation of the left atrium. The pulmonary artery and its branches appeared to be markedly dilated. The lung fields exhibited almost normal transparency. There was no evidence of pulmonary emphysema. The electrocardiogram showed high P waves and right axis deviation. Serology tests for syphilis were negative. The urine showed traces of albumin.

At first the patient responded favorably to treatment with digitalis and diuretics. On 2 occasions syncopal attacks occurred at night. Once after such an attack a bradycardia of 64/min. was noted, while the usual heart rate of the patient observed during the day was around 90/min. On the 8th hospital day fever and severe cough developed, and the patient's condition deteriorated rapidly. Numerous râles were persistently heard over the lungs, and the sputum became hemorrhagic. Finally the patient became somnolent and died on the 26th hospital day.

Diagnosis. The clinical diagnosis was mitral stenosis with secondary pulmonary arteriosclerosis. Postmortem study revealed marked hypertrophy and dilatation of the right ventricle. The valves were normal. Extensive, marked arteriosclerosis was found in both the larger and small pulmonary arterial branches, and in the arterioles. Some branches of the pulmonary artery were filled with canalized thrombi. A recent hemorrhagic infarction was present in the left lung. There was purulent bronchitis, especially pronounced in the left lung. The medium sized and small bronchi showed inflammatory changes with proliferation of the mucous membranes, partly obstructing the bronchial lumen. There was no evidence of pulmonary emphysema nor were there any changes suggestive of syphilis.

Case 2. G. N., a 26-year old housewife, was admitted to the hospital for the first time on January 10, 1950. She complained mainly of fainting attacks which she had repeatedly experienced for the past 5 years. Until the age of 20 she was able to run and to do strenuous work without experiencing discomfort. Her first fainting attack occurred in her 20th year when she ran after a bus. Thereafter she fainted about twice or 3 times a week, and the attacks were invariably precipitated by effort. They were not associated with tongue bite or convulsions. Light-headedness or dizziness usually heralded the approaching attack and compelled the patient to slow down. After she had experienced the ill effects of undue exertion she learned to avoid syncopal attacks by adjusting her pace of work. She was able to climb stairs without losing consciousness when she walked slowly enough. She complained of mild exertional dyspnea but there was no orthopnea. One and one-half years prior to admission the patient had a miscarriage in the 4th month of pregnancy. There was no history of rheumatic fever or chorea.

Physical Examination. The patient was a short, obese woman of ruddy complexion. She presented neither cyanosis nor clubbing of the fingers. There was no edema. Dyspnea was absent during rest. The cervical veins were not distended. The lungs were clear. The precordial region showed no bulge or abnormal pulsations. The apex beat of the heart was not palpable. No thrills were felt. Percussion revealed a normal area of cardiac dullness. No murmurs were heard. The second pulmonary sound was accentuated and split. The heart action was regular; its rate was 72/min. The blood pressure was 120/70 mm. The liver and spleen were not palpable.

Laboratory Findings. The urine was normal. Blood examination showed: hemoglobin, 13 gm.; red blood cells, 4,550,000; white blood cells, 8000, with normal differential count; blood glucose, 60 mg./100 cc.; blood urea nitrogen, 20 mg./100 cc.; total serum protein, 8.7 gm./100 cc.; albumin, 4.7 gm.; globulin, 4.0 gm. Total serum cholesterol was 212 mg./100 cc. Blood calcium was 9.0 mg./100 cc.; phosphorus, 3.6 mg./100 cc.; alkaline phosphatase, 4.3 KA units. The cephalin flocculation test was negative. The serology test for syphilis was negative. Venous pressure in the arm was 100 mm. of water; after pressure in the hepatic region it was 110 mm. Arm-to-tongue circulation time

(with decholin) was 19 seconds; ether time was 13 seconds.

Roentgen study (Fig. 1) revealed a marked prominence of the pulmonary conus and dilatation of the large pulmonary artery branches on the right side without evidence of pulmonary congestion. In the right anterior oblique view the outflow tract of the right ventricle appeared to be enlarged. There was no evidence of dilatation of the left atrium. The electrocardiogram (Fig. 2) was suggestive of right ventricular hypertrophy.

Attempts to produce syncope by carotid sinus pressure or hyperventilation failed. It was not possible to persuade the patient to exercise until syncope developed. She was

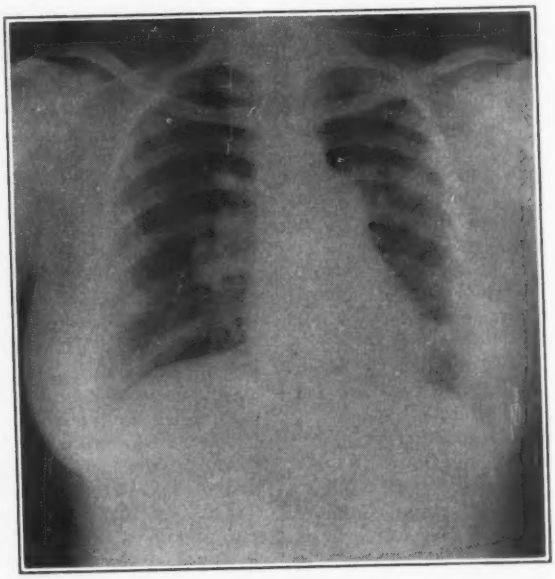

FIG. 1. (CASE 2)—The pulmonary arch is prominent, and the pulmonary branches in the right hilar region are almost aneurysmally dilated. Pulmonary congestion is absent.

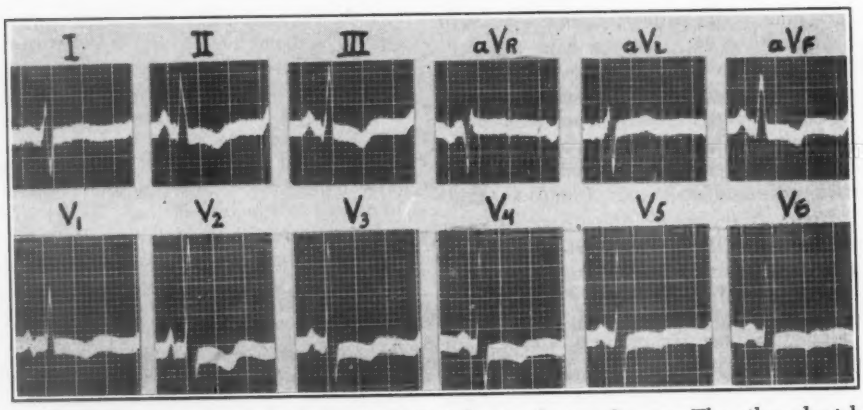

FIG. 2. (CASE 2)—Lead V_1 shows a prominent R deflection but no S wave. The other chest leads present an S deflection which increases toward the left side of the precordium. T is inverted in all chest leads. The changes suggest right ventricular hypertrophy.

exceedingly apprehensive, and after making several trips on the 2-step staircase she was pale and distressed, complained of palpitation, and refused to continue the test.

The significant clinical features were: evidence of right ventricular hypertrophy as indicated by electrocardiographic and roentgenologic signs; dilatation of the pulmonary artery and its main branches; accentuation of the second pulmonary sound suggesting increased tension in the lesser circulation; absence of signs of pulmonary congestion, dilatation of the left atrium, or enlargement of the left ventricle. A rheumatic history was lacking. No murmurs could be heard characteristic of rheumatic valvular disease or of congenital heart disease. Absence of pulmonary congestion and hilar dance were against interatrial septal defect. There was no evidence of structural disease of the lung. Therefore a clinical diagnosis of primary pulmonary arterial disease was made.

Physiological studies by means of cardiac catheterization* revealed no evidence of shunt. The blood pressure in the pulmonary artery was markedly increased and even slightly above that measured in the brachial artery. The oxygen saturation of the arterial blood was normal and did not change after exercise. Thus physiological studies confirmed the clinical impression of primary pulmonary artery disease and revealed the presence of marked pulmonary hypertension.

The patient was admitted to the hospital for the second time on October 22, 1950. Since July, 1950, she had complained of frequent nausea and vomiting. When she walked out from the house she experienced a pressing sensation in the precordium which subsided when she rested. She said that she had occasionally felt similar discomfort previously as far back as 1948. During the past 2 months the sensation of pressure in the chest had not recurred; instead, she often felt nausea upon exertion, and after climbing 3 flights of stairs to her apartment she vomited. There was evidence of congestive heart failure. The venous pressure in the arm measured 180 mm. of water and rose to 250 mm. after pressure in the hepatic region. However, cyanosis and polycythemia were absent. The systemic arterial pressure, which had been normal during the first hospitalization, showed an increase of the diastolic values. Repeated measurements yielded figures for the systolic pressure ranging from 110 to 130, while those of the diastolic pressure varied from 96 to 110 mm. of Hg.

During the second hospitalization a syncopal attack was observed which developed during an exercise test.† The unconscious state lasted somewhat longer than a minute. Pulse and heart sounds disappeared. After recovery the heart action was for some time slow and irregular. There was no chance to study the heart action by electrocardiographic record during and immediately after the state of unconsciousness.

Congestive heart failure advanced in the following months. The patient died at home 17 months after the first admission. Postmortem examination was not performed.

Case 3. M. K., a 34-year old housewife, was admitted to the hospital on July 17, 1950, for study of the cause of her fainting attacks. She had always enjoyed good health. She had been active in athletics such as handball playing, bicycle riding, swimming. As late as the summer of 1948 she played handball and enjoyed it greatly. In August, 1948, she fainted once when she hurried up 2 flights of stairs to look after her crying baby. Later on she suffered about a dozen syncopal attacks, some of which occurred at night. Once she was awakened by her crying baby; while bending over the crib she lost consciousness. Another time she went to the bathroom at night. After returning to bed and lying comfortably, she became bathed in perspiration and felt nauseated. At one time syncope occurred when she helped her husband to push the baby carriage a short distance uphill. Although she had been accustomed previously to a very active life, she now avoided undue effort and used every chance to sit down and rest. She found out that brisk effort following a period of rest was especially obnoxious. Once after having watched television she got up, started to undress, and fainted. "I am like a motor that has to be warmed up," the patient said. She learned to go slowly to work, and once she was "warmed up" she could stand a good deal of effort.

The last attack of syncope which led to her hospitalization occurred 3 days prior to

* The physiological studies in Cases 2 and 3 were conducted in the cardio-pulmonary laboratory at the Maimonides Hospital by Drs. D. T. Dresdale, M. Schultz, and R. J. Michtom and are being published elsewhere.

† The test was performed in the cardio-pulmonary laboratory, and the syncopal attack was observed by Dr. M. Schultz.

her admission. While she was in a friend's house she heard her baby crying in a room which was one flight upstairs. Aware of the consequences of brisk effort she allowed her friend to rush upstairs and she followed slowly. She was tense, however, and after reaching the top of the flight of stairs she lost consciousness so suddenly that she struck her face against the knob of the door and developed a black eye. Usually the patient felt the impending attack for a split second. She felt breathless and choked. "I cannot get enough air and the room begins to sparkle." She knew that one further step to reach a chair would bring on syncope. Only instantaneous immobilization could avert an attack. During the attacks there was involuntary loss of urine. Afterwards the patient felt miserable; she was nauseated and perspired profusely. Almost every attack was followed by diarrhea; vomiting occurred when the stomach was filled.

After the patient had suffered the first 2 syncopal attacks within a period of 5 months, she was studied in a consultation clinic of a University hospital in New York in January and February, 1949. Negative findings were reported. There was no abnormal sensitivity of the carotid sinus. Roentgen study failed to reveal cardiovascular abnormality. Psychoneurosis and hysteria were diagnosed. Petit mal was also considered. Because the syncopal attacks recurred, a neurologist was consulted in August, 1949. Hyperventilation syndrome was diagnosed and the patient was advised to avoid deep breathing. An electroencephalogram taken in January, 1950, was negative.

During childhood the patient had measles, chickenpox, and scarlet fever. There was no history of rheumatic fever or chorea. The patient went through 2 uneventful pregnancies in 1942 and 1947. The family history of the patient revealed that her father, the father's brother, and her mother had suffered from high blood pressure. A brother of the patient, 26 years old, also had high blood pressure. Another brother had suffered rheumatic fever and was said to have a heart murmur.

Physical Examination. The patient was a rather obese woman who did not appear seriously ill. She showed neither cyanosis nor clubbing of the fingers. Dyspnea and edema were absent. The cervical veins were not distended. The lungs were clear. In the precordial area a systolic heaving pulsation was felt to the left of the sternum between the 3rd and 5th ribs. The apex beat was not distinctly palpable. In the 3rd left intercostal space marked dullness was percussed which extended from the left sternal margin about 1½ inches to the left. No abnormal dullness was observed in the sternal area. The heart sounds were fair. The 2nd pulmonary sound was accentuated. No murmurs were heard. The cardiac action was regular; its rate was 104/min. The blood pressure was 126/94 mm. of Hg on the day of admission; 4 days later it measured 130/104 mm. and after excitement it rose to 160/110 mm. of Hg. In the following days it was normal again. The liver extended almost to the umbilical line. The spleen was not palpable.

Laboratory Findings. The urine was normal. Blood examination showed: hemoglobin, 14.5 gm.; hematocrit, 49; red blood cells, 5,100,000; white blood cells, 10,000 with normal differential count; fasting blood sugar, 75 mg./100 cc.; urea nitrogen 13 mg./100 cc.; total serum protein, 6.3 gm./100 cc.: albumin, 4.0 gm.; globulin, 2.3 gm.; alkaline phosphatase, 5.8 KA units. The icteric index was 7.9 units. The serologic test for syphilis (Mazzini) was negative. Venous pressure in the arm was 200 mm. of water, rising to 225 mm. after pressure in the hepatic region. Arm-to-tongue circulation time (with decholin), 25 seconds; ether time was 4 seconds.

Roentgen study of the chest (Fig. 3) revealed an enlarged heart with prominent pulmonary arch. The main branches of the pulmonary artery appeared also to be dilated, but the pulmonary vascular markings in the peripheral portions of the lungs were diminished in intensity. In the oblique views there was evidence of enlargement of both the inflow and outflow tracts of the right ventricle. The left atrium was not dilated.

The electrocardiogram (Fig. 4) showed changes suggestive of atrial and right ventricular hypertrophy. No significant changes of the electrocardiogram were noted following an exercise test which consisted of 25 trips on a 2-step staircase. The patient performed the test slowly, ever conscious of the danger of syncope. She stopped twice for a few seconds.

The history of syncopal attacks on effort, in association with an accentuated second pulmonary sound and evidence of right ventricular hypertrophy, which was not accounted for by the usual causes, suggested primary pulmonary hypertension. There was no rheumatic history. No murmurs were heard suggestive of congenital heart disease or rheumatic valvular lesions. Lack of pulmonary congestion and of hilar dance was against

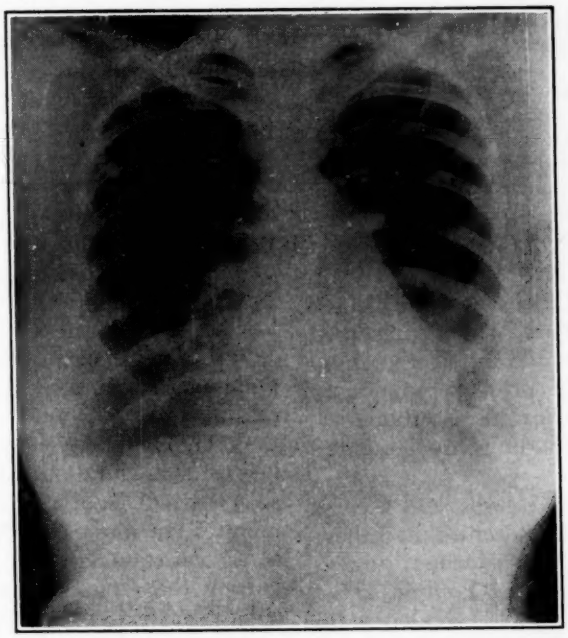

FIG. 3. (CASE 3)—The cardiac silhouette is enlarged and the pulmonic arch is prominent. The vascular markings are accentuated in the hilar region but are diminished in the peripheral portions of the lungs.

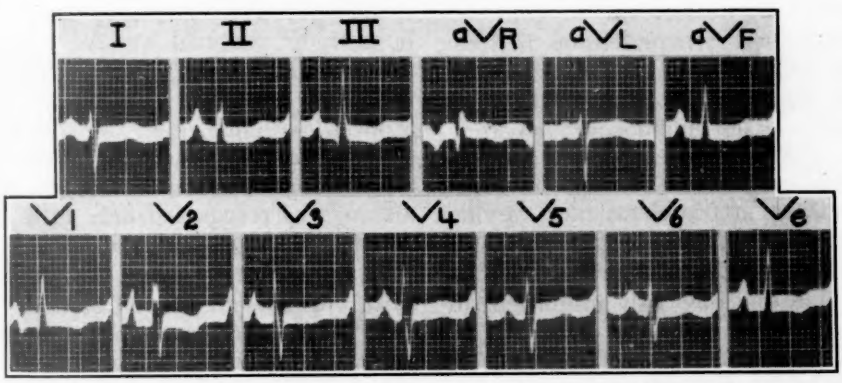

FIG. 4. (CASE 3).—The P waves are rather large in Leads II and III and in the right side precordial leads. There is right axis deviation. Lead V_1 presents a Q wave and a prominent R deflection. In leads from the left side of the precordium the S deflections are larger than the R waves. The changes suggest atrial and right ventricular hypertrophy.

interatrial septal defect. Absence of enlargement of the left atrium and of pulmonary congestion spoke against mitral stenosis. There was no evidence of structural disease of the lungs which might affect the pulmonary arterial pressure.

Physiological study by cardiac catheterization revealed no evidence of shunt. The pressure in the pulmonary artery was markedly increased. Thus, clinical and laboratory evidence pointed to primary pulmonary artery disease with marked increase of the tension in the lesser circulation.

In addition to the 3 cases reported here, 6 cases were collected from the literature which presented syncopal attacks and fitted the diagnostic pattern of primary pulmonary hypertension. Their clinical, laboratory, and postmortem findings are presented in Table 1.

Discussion. Our 3 cases, and 6 cases collected from the literature, had these features in common: syncopal attacks precipitated by effort; dilatation of the pulmonary artery and evidence of right ventricular hypertrophy; and absence of the common causes of right ventricular hypertrophy, especially of rheumatic valvular lesions, congenital heart disease, and chronic pulmonary disease. These features suggest primary pulmonary hypertension. In 3 patients (Cases 2, 3, 9) physiological study by cardiac catheterization revealed marked pulmonary hypertension. Postmortem examination which was performed in 7 cases revealed pulmonary arteriosclerosis of varying degree. At least in 2 instances (Cases 7 and 9) pulmonary arteriosclerosis was mild and obviously insufficient to explain right ventricular hypertrophy. Of particular interest is Wittenberg's[20] case in which study by cardiac catheterization revealed marked hypertension in the lesser circulation, and postmortem examination failed to show arteriosclerosis of the pulmonary arteries and arterioles of sufficient extent to account for right ventricular hypertrophy.

SYNCOPE. Besides right ventricular hypertrophy and dilatation of the pulmonary artery, syncopal seizures were an outstanding feature in the cases summarized in this report. The attacks of syncope were similar in many ways to those of angina pectoris, notably with regard to the precipitating factors. Running for a bus, pushing a carriage uphill, climbing upstairs, and excitement were likely to produce attacks. In advanced stages of the disease lesser effort was followed by loss of consciousness.

Syncope was often preceded by premonitory symptoms: light-headedness, dizziness, a feeling of epigastric fullness, choking or tightening about the heart. The duration of unconsciousness varied from a few seconds to minutes. In one case (No. 6) the unconscious state lasted for 25 minutes. During the attacks cyanosis and muscular rigidity were often present. Some patients were incontinent. No tongue bite was reported. The attacks were often followed by nausea, vomiting, abdominal cramps, and diarrhea. After seizures of syncope the patient felt weak and nervous for some days. The number of syncopal attacks suffered throughout the course of the disease varied in individual cases from 2 to a dozen or "innumerable".

The causal relationship between syncopal attacks and pulmonary vascular disease was recognized only in a few cases[4,6]. Errors in interpretation are common, especially when syncopal attacks precede the manifestations of right ventricular hypertrophy and dilatation of the pulmonary artery as occurred in Case 3 of this report. Neurosis and hysteria were erroneously diagnosed. Some patients were referred to the neurologist because epilepsy was suspected. In one case a diagnosis of the hyperventilation syndrome was made.

TABLE 1.—CASES OF PRIMARY PULMONARY HYPERTENSION WITH SYNCOPAL ATTACKS, COLLECTED FROM THE LITERATURE

TABLE 1.—CASES OF PRIMARY PULMONARY HYPERTENSION WITH SYNCOPAL ATTACKS, COLLECTED FROM THE LITERATURE

Case No.	*Author*	*Sex*	*Age at Time of Death*	*Syncope*	*Cyanosis*	*Cardiac Catheterization*	*Postmortem Findings*
4	McCallum[13]	♀	39	Syncopal seizures associated with effort began 15 years prior to death	Moderate		Hypertrophy and dilatation of right heart chambers. Marked pulmonary arteriosclerosis and arteriolosclerosis, with secondary thrombosis
5	Brenner[4]	♂	11	Syncopal attacks with drowsiness, muscular rigidity, and incontinence	Slight		Hypertrophy and dilatation of the right ventricle. Extensive pulmonary arteriosclerosis. Endarteritis obliterans of small pulmonary arteries
6	Killingworth and Gibson[11]	♂	10	Syncopal attacks associated with effort began 6 months before death. One attack of unconsciousness lasted for 25 minutes	None		Hypertrophy of right ventricle. Dilatation of large pulmonary arteries. Proliferative intimal sclerosis in small pulmonary arteries with narrowing or occlusion of arterioles. Microscopic pulmonary atelectasis and emphysema
7	De Navasquez and Assoc.[6] (Case 2)	♂	30	Syncopal attacks began 1 year before death; they were caused by running, carrying a load upstairs, or attending to child at night	Present		Extreme right ventricular enlargement. Dilatation of pulmonary artery. Atheromatous intimal thickening in larger pulmonary arteries, insufficient to explain right ventricular hypertrophy
8	Nellen[16]	♀	26	Syncopal attacks on running upstairs or after taking a hot bath	Extreme in the final stage o the disease	No evidence of shunt. Pressure in the right atrium and ventricle increased	Dilatation and hypertrophy of the right ventricle. Extensive pulmonary atherosclerosis with thrombi in large and small branches. Medial hypertrophy and narrowing of smallest pulmonary arteries
9	Wittenberg[20]*	♀	53	Innumerable syncopal attacks during a period of 18 months preceding death. The attacks were invariably precipitated by effort	Moderate	No evidence of shunt. Pressure in the pulmonary artery: systolic 78 to 83 mm.Hg; diastolic 40 to 44 mm.Hg	Hypertrophy of the right heart chambers. Moderate arteriosclerosis of the pulmonary arteries, with slight involvement of the pulmonary arterioles, insufficient to explain right ventricular hypertrophy

* The author is indebted to Dr. S. J. Wittenberg for permission to use the data of his case.

The mechanism of the syncopal attacks which occur in the presence of pulmonary vascular disease is poorly understood. The view has been expressed that syncope is related to cyanosis and is due to cerebral anoxia resulting from inadequate oxygenation of the blood in the lungs[6,11]. However, cyanosis was absent in some of the patients suffering from syncopal attacks, and the oxygen saturation of the arterial blood, determined in Cases 2 and 3, was normal[7].

Syncopal seizures rarely lent themselves to accurate observation. In Case 6 an attack of unconsciousness was reported which lasted for 25 minutes. The heart rate was 160 and the pulse was imperceptible. Breathing was rapid. There were cyanosis and cold perspiration. It is uncertain whether this prolonged state of unconsciousness was representative of the syncopal attacks characteristic of the condition under consideration, since in other instances the attacks usually lasted only for a few seconds or minutes. In Case 1 a bradycardia of 64/min. was observed immediately after a syncopal attack suffered at night, while the average pulse rate of the patient recorded during the day time was 90/min. In Case 2 it was possible to watch a seizure of syncope that developed during an exercise test. Neither pulse nor heart sounds were present during the unconscious state. After recovery the heart action remained slow and irregular for some time. If this attack is representative of the whole group, observation and experience derived from animal experiments suggest that syncope is of the vaso-vagal type. It is possibly due to a reflex mechanism that originates in the wall of the pulmonary artery. The latter is known to possess neuroreceptors similar to those present in the wall of the aorta[3,5,19]. In the experimental animal it is possible to produce fall of the systemic arterial pressure and slowing of the heart rate by raising the pressure in the pulmonary artery[5,19]. This effect cannot be produced after cutting the pulmonary branches of the vagus nerve. A similar mechanism might be called into play when patients suffering from marked pulmonary hypertension are subject to effort or excitement.

Effort syncope seems to be a characteristic feature of *primary* pulmonary hypertension. To our knowledge it does not occur in instances of pulmonary hypertension secondary to chronic pulmonary disease, valvular lesions, or congenital heart disease. To be sure, loss of consciousness infrequently occurs in cases of chronic pulmonary disease during severe coughing spells, but not in association with efforts of other kind or with excitement. Tussive syncope is thought to be caused by the Valsalva effect which results in diminished blood flow to the heart and cerebral anemia[14]. Effort syncope is not an invariable feature of primary pulmonary arterial disease. It was absent, for instance, in 3 cases of pulmonary hypertension reported by East[8], and in 1 of 2 cases observed by Nellen[16], and by De Navasquez and associates[6], respectively. During the past 2 years we had occasion to observe 4 patients in whom the diagnosis primary pulmonary arterial disease with right ventricular hypertrophy was made. Two of the patients (Cases 2 and 3), in whom cardiac catheterization revealed marked pulmonary hypertension, had frequent attacks of effort syncope. In 2 other cases, in which postmortem examination revealed extensive, obstructive pulmonary arterial disease, syncope was absent. We do not know whether the variation in the incidence of syncopal attacks is due to a difference in the basic pathologic condition or

perhaps to a varying individual reaction. It is known, for instance, that the sensitivity of the carotid sinus reflex varies greatly, and that no response to pressure is obtained in 30% of normal individuals. On the other hand, the sensitivity of the carotid sinus reflex is greatly enhanced in the presence of systemic hypertension or arteriosclerosis[3].

In utilizing syncope as a diagnostic symptom of primary pulmonary artery disease, it must be borne in mind that attacks of loss of consciousness may occur in a variety of heart diseases. Cardiac disturbances produce syncope by interruption or undue slowing of the heart beat, by reducing the cardiac output, or by large veno-arterial shunts. The first and largest group responsible for spells of loss of consciousness is that of disordered cardiac rhythm. Atrio-ventricular block, sinus arrest, sino-auricular block, paroxysmal tachycardia, including auricular and ventricular flutter and fibrillation, may be attended by attacks of syncope. The carotid sinus syndrome and nervous vaso-vagal syncope belong in this group also since they are associated with abnormal slowing of the heart beat. In a second group of heart diseases, acute failure of the left ventricle is probably responsible for syncopal attacks. This group comprises advanced aortic stenosis and acute myocardial infarction. A third group includes ball-valve thrombi and tumors of the atrium which, by obstructing the atrio-ventricular ostia in certain body postures, may give rise to loss of consciousness. A fourth group is represented by certain congenital cardiac lesions of the cyanotic group. In these a large veno-arterial shunt increases during effort and diminishes the oxygen saturation of the arterial blood to an extent incompatible with maintenance of adequate cerebral function.

The precipitating factor of effort distinguishes syncope of primary pulmonary arterial disease from nervous vaso-vagal syncope and from attacks of unconsciousness associated with most of the cardiac disorders. Effort syncope is encountered only in 3 forms of heart disease: aortic stenosis, congenital heart disease with veno-arterial shunt, and occasional instances of Adams-Stokes syndrome due to heart block. The differential diagnosis of these conditions and primary pulmonary hypertension should not prove difficult. Aortic stenosis is characterized by the typical murmur and by evidence of left ventricular hypertrophy. Congenital heart disease with syncope is usually of the cyanotic type and becomes manifest in early childhood, whereas primary pulmonary arterial disease is acyanotic until the terminal stage and, in the majority of cases, is a disease of adult life. In those instances in which it affects young children, physiologic studies may be required to differentiate primary pulmonary artery disease from congenital cardiac lesions. The finding of diminished oxygen saturation of the arterial blood will usually support a diagnosis of veno-arterial shunt rather than primary pulmonary artery disease. Patients suffering from Adams-Stokes attacks frequently present symptoms and signs of coronary artery sclerosis, evidence of left ventricular enlargement, and electrocardiographic signs of atrioventricular or intraventricular conduction disturbance.

Thus syncope precipitated by effort is a significant diagnostic feature of primary pulmonary hypertension. It is highly suggestive of this condition if associated with one or more of the following signs: dilatation of the pulmonary artery, accentuation and split-

ting of the pulmonary second sound, and evidence of right ventricular hypertrophy. The diagnostic value of syncope is enhanced by the fact that it is sometimes an early manifestation and makes a correct diagnosis possible before congestive heart failure has developed. In 4 cases of our series (Nos. 1 to 4) syncope occurred from 2 to 14 years prior to death. In one case (No. 3) syncopal attacks developed 2 years prior to admission and preceded the roentgenologic and electrocardiographic manifestations of right ventricular hypertrophy. The view has been expressed often that the early stages of pulmonary arteriosclerosis are unknown and that the symptoms of the disease are essentially those of right heart failure[4,9,17]. Knowledge of the significance of syncopal attacks may allow (at least in some cases) an earlier diagnosis and perhaps, eventually, the discovery of means of arresting the relentless progression of the disease.

Cyanosis. Severe cyanosis is generally held to be an important diagnostic sign of primary pulmonary arterial disease[4,10,21]. Lack of cyanosis has, as a matter of fact, been considered sufficient reason for abandoning an otherwise well-founded diagnosis of primary pulmonary arteriosclerosis[11]. This view is not supported by analysis of the cases in this report. Cyanosis was slight or moderate in 4 cases, including Brenner's case, which is considered as representative of primary pulmonary arteriosclerosis of marked degree. Cyanosis was not observed in 2 patients (Cases 2 and 3) 2 and 5 years, respectively, after the onset of symptoms. Cyanosis was absent in Case 6 except during attacks of syncope. In one instance (Case 8) cyanosis was slight to moderate during the course of the disease and grew more intense in the terminal stage. In Case 7 cyanosis was observed when the patient was first examined, 3 days prior to death. Thus it appears that severe cyanosis is neither a constant nor an invariable feature of primary pulmonary arterial disease. It rarely appears before the disease has entered its terminal stage. Therefore, lack of cyanosis should not invalidate an otherwise well-founded diagnosis of primary pulmonary arterial disease. Brenner[4] has pointed out that no adequate explanation could be offered for the presence of marked cyanosis in cases of pulmonary arteriosclerosis, since narrowing or occlusion of the arterioles did not interfere with proper oxygenation of the blood in the lungs.

Summary. Three cases of primary pulmonary arterial disease are reported, and 6 cases of the literature are reviewed. All cases had these features in common: 1) Syncopal attacks precipitated by effort; 2) evidence of right ventricular hypertrophy in the absence of known causes, particularly of rheumatic valvular lesions, congenital heart disease, or chronic pulmonary disease; 3) dilatation of the pulmonary artery without evidence of congestion in the lungs; 4) accentuation of the second pulmonary sound; 5) absence of signs of syphilis.

Postmortem data were available in 7 cases. Arteriosclerosis of the pulmonary arteries was present in all instances but varied in degree. In 2 instances pulmonary arteriosclerosis was trivial and obviously inadequate to account for the hypertrophy of the right ventricle. In one of the latter, cardiac catheterization had shown marked increase in the pressure of the pulmonary artery. In 2 patients, in whom postmortem findings were not available, marked pulmonary hypertension was revealed by catheterization. Facts were discussed which strongly suggested that the primary lesion in the cases of this report was

essential hypertension in the lesser circuit.

The mechanism of the syncopal attacks in cases of primary pulmonary hypertension is not sufficiently understood. Certain observations suggest that syncope is due to a reflex mechanism which originates in neuroreceptors in the wall of the pulmonary artery and uses the vagus nerve as afferent pathway; it results in fall of the systemic blood pressure and inhibition of the heart beat.

Effort syncope is not an invariable feature of the cases of primary pulmonary hypertension. When present, it is a very useful diagnostic sign. Combined with evidence of right ventricular hypertrophy or dilatation of the pulmonary artery, or both, it is highly suggestive of primary pulmonary hypertension. The diagnostic value of effort syncope is enhanced by the fact that it may allow early diagnosis before congestive failure or even manifestations of right ventricular hyper trophy have appeared.

Severe cyanosis, usually quoted as an important and even indispensable sign of obstructive pulmonary arteriosclerosis, is neither a constant nor an invariable feature of the disease; its diagnostic value has been greatly overrated.

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PLACENTAL SERUM THERAPY FOR RHEUMATOID ARTHRITIS

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With the advent of cortisone and ACTH into the field of therapy for the rheumatic and collagen diseases[4], there has been a marked upsurge of interest in the treatment of rheumatoid arthritis. However, in spite of the remarkable results obtained from these hormones, they have some definite drawbacks, that is, toxicity, high cost, and short duration of effects. As a result physicians have been experimenting with related drugs which ideally would have all the advantages and none of the disadvantages of cortisone and ACTH. To date the results with other substances have shown minor or questionable results.

It has been known for some time that pregnancy has an ameliorating effect on rheumatoid arthritis[3]. Barsi[1] of England treated several patients suffering from rheumatoid arthritis with transfusions of blood taken from pregnant women. He reported excellent results, but these have not been confirmed in this country. Recently Granirer[2], used plasma obtained from postpartum women for the therapy of rheumatoid arthritis and reported good results. The difficulty lies in obtaining blood from postpartum patients.

As the pregnant woman apparently develops substances which are of therapeutic value against rheumatoid arthritis and related diseases, it occurred to us in August, 1949, that these substances might be present in the placental circulation. We began collecting blood, therefore, from the placenta and using the serum for the treatment of rheumatoid arthritis.

Method. Obtaining Placental Serum. The serum was supplied by one of us (M.L.) from the Central Maternity Hospital. The technique of collecting the blood is simple. When the baby is born, it is allowed to take one or two deep breaths; the cord is then immediately clamped and cut, and the baby put aside. The bottle with the needles (Figs. 1 and 2), which had been previously sterilized and placed on the delivery room table, is now ready for use. The area on the umbilical cord, close to the clamp, where the needle is to be inserted, is sprayed with ether. The needle is inserted into the umbilical vein, the suction bulb is compressed, and the blood flows into the bottle. The amount of blood collected varies from 20 cc. to 200 cc. (average, about 70 cc.). The blood is placed in the refrigerator for 3 to 5 days. The supernatant serum is then poured off into a sterile bottle and pooled, and is ready for use. We obtain about 30% serum from the blood. The serum is poured off through a sieve-covered funnel so as to prevent clotted blood from dropping into the bottle. When using the serum, the bottle is shaken to insure uniform distribution of the active principal. Once the apparatus is set up, the serum is available at practically no cost.

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METHOD OF TREATMENT. We initiated our work by using placental plasma but found that better results were obtained by using placental serum. Each of our patients received 10 cc. of this serum, intramuscularly, twice a week. The serum was kept under constant refrigeration and used with sterile technique.

All the patients in this group had active rheumatoid arthritis. Our criteria for activity were based on clinical findings, both objective and subjective, Roentgen-ray evidence of rheumatoid arthritis, and an elevated sedimentation rate. Most of the patients had received

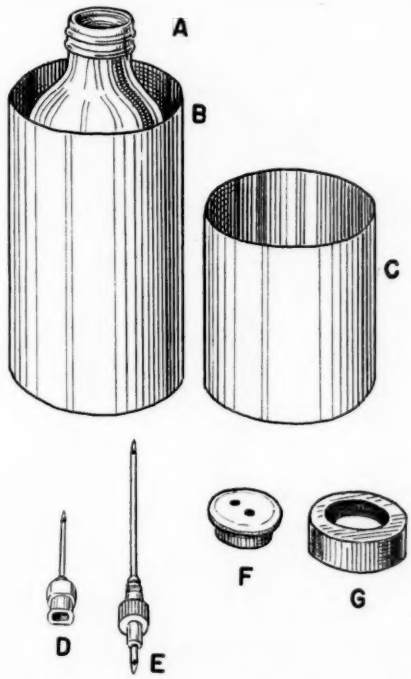

FIG. 1.—The bottle A is placed in a metal container B to be autoclaved. The rubber stopper F and the cap G are placed on a tray and are sterilized at the same time. When the sterilization is completed the stopper F and G are placed on the bottle under aseptic precautions and container B is covered by C.

The needles D and E are placed in a small envelope and with the suction bulb, S, are placed in a paper bag to be autoclaved. The metal adapter on the end of the tubing of S is covered with a small envelope so that it does not burn the rubber bulb when hot. These are sterilized with other rubber goods.

Results. This report is based on our results in treating 33 cases of active rheumatoid arthritis and 2 cases of Marie-Strumpell's disease for periods varying from 3 months to 1 year. The ages of our patients varied between 23 and 74, approximately 80% being over the age 45. Thirty of the 35 patients were women.

previous therapy with gold, hormones, physiotherapy, salicylates, or other drugs with either slight or no improvement. All were ambulatory and in our table they are classified according to the standards of the New York Rheumatism Association. The severity of the disease was graded from Stage 1, or early, to Stage 4, or terminal, and

the function from Class 1, or complete function, to Class 4, or completely incapacitated. The results of treatment were graded from 1, or complete remission, to Grade 4, or no improvement[5].

Our results were not so rapid or so spectacular as those reported with ACTH and cortisone. The degree and rapidity of improvement depended on the duration and the severity of the disease. The results were better in the more recent cases and in the younger age group. Definite, although slow, improvement did occur, however, in over 85% of the patients. With our method we noted beginning improvement following the 4th or 5th injection, improvement which would continue 1 or 2 days. After the patients had received from 20 to 40 biweekly injections, we were able to lengthen the interval between injections to 1 week in about ¼th of our patients. In 9 cases we induced apparent clinical remissions lasting 1 to 6 months. In those patients who then relapsed, retreatment again yielded good results.

There was moderate reduction of subjective stiffness and pain, pain on motion, and articular tenderness in every case. Slight to moderate reduction of joint swelling, particularly of the proximal interphalangeal joints, occurred in 85 to 90% of the patients. There was a moderate increase of muscle strength and joint function, limited by destructive changes, in over 85% of our cases. In addition almost all of the patients had an improved appetite, slept better, and had an in-

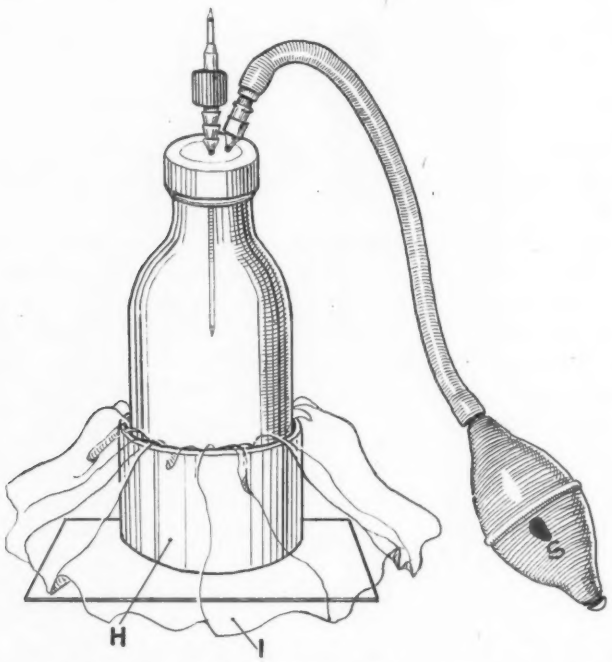

FIG. 2.—At the time of a delivery, the bottle is removed from the container and placed on the sterile instrument table, as are also the needles and the suction bulb S. They are connected as shown. The bottle is set in a stand H which is under the sterile sheet. The apparatus is ready for use.

TABLE 1.—RESULTS WITH PLACENTAL SERUM THERAPY

Pt.	*Sex*	*Age*	*Duration (yr.)*	*Disease*	*Stage*	*Class*	*Response*	*Comments*
M. 1	F	74	1½	Rheumatoid Arthritis	3	2	2	Maintained on weekly inject. after about 25 inject.
G. S. 2	F	68	5	"	3	2	2	Required bi-weekly maint. inject.
G. N. 3	F	55	4	"	2	2	2	On weekly inject. after about 35 inject.
W. 4	F	74	7	"	3	3	3	Required bi-weekly maint. inject.
M. H. 5	F	72	2	"	2	2	2	Required bi-weekly maint. inject.
N. Y. 6	M	53	15	"	3	3	3	Required bi-weekly maint. inject.
C. C. 7	F	74	7	"	2	2	3	Required bi-weekly maint. inject.
P. B. 8	F	45	1	"	3	3	2	Maintained on weekly inject.
C. M. 9	F	49	3 mo.	"	2	2	2	Had a clinical remission for 3 mo. after 25 inject.
Y. L. 10	F	57	6½	"	2	2	2	After 18 inject. had a clinical remission lasting 6 mo.
V. 11	M	46	6	"	4	2	2	After about 60 inject. maintained on weekly inject.
W. J. 12	F	40	3 mo.	"	2	2	2	After 10 inject. had a clinical remission which has persisted
B. 13	F	55	6½	"	2	2	4	Not improved
L. G. 14	F	58	6½	"	2	2	3	Required bi-weekly maint. inject.
M. L. 15	F	48	1	"	2	2	2	Clinical remission after 8 inject.
E. L. 16	F	55	5	"	2	2	2	Required bi-weekly maint. inject.
S. 17	F	55	4	"	2	2	3	Required bi-weekly maint. inject.
A. C. 18	F	51	2	"	2	2	2	Clinical remission after about 40 inject.
L. R. 19	F	50	3	"	2	2	2	On weekly inject. after 44 inject.

TABLE 1.—(*Continued*)

Pt.	*Sex*	*Age*	*Duration (yr.)*	*Disease*	*Stage*	*Class*	*Response*	*Comments*
E. C. 20	F	23	5	Marie Strümpell's Disease	3	3	2	Clinical remission for 6 mo.; relapse and remission after retreat.
W. 21	M	59	5	Rheumatoid Arthritis	2	2	2	Clinical remission
R. M. 22	M	57	5	"	3	3	4	Failure. Responded to cortisone
D. C. 23	F	64	10	"	2	2	2	On weekly inject.
E. M. 24	F	60	10	"	2	2	2	Maint. on weekly inject. after 21 inject. bi-weekly
B. M. 25	F	72	4 mo.	"	2	2	2	Maint. on weekly inject.
I. G. 26	M	38	6	Marie Strümpell's Disease	3	3	2	Remission lasting 1 mo.
M. 27	F	50	5	Rheumatoid Arthritis	2	2	2	Remission lasting 6 mo.
H. 28	F	65	15	"	2	2	4	Non-improved
29	F	69	15	"	4	2	4	Non-improved
30	F	41	9	"	3	2	2	Required bi-weekly maint. inject.
W. 31	F	60	6	"	2	2	3	Required bi-weekly maint. inject.
A. C. 32	F	69	15	"	3	2	2	After 12 inject. maint. on weekly inject.
R. W. 33	F	63	15	"	3	3	2	Required bi-weekly maint. inject.
C. 34	F	44	4	"	4	2	3	Required bi-weekly maint. inject.
S. 35	F	58	6 mo.	"	2	2	3	Required bi-weekly maint. inject.

TABLE 2.—SUMMARY OF THERAPEUTIC RESPONSE TO PLACENTAL SERUM INJECTIONS IN 35 PATIENTS

Response, grade	*Patients*	*%*
1	0	—
2	23	65
3	8	23
4	4	12

creased sense of well being. The elevated sedimentation rate was decreased in 25% of the patients, but in none did it become normal. In this group of cases there were no complete remissions and 4 unimproved cases.

CONTROL. For control observations, 2 different methods were used. One was to start a patient on pooled non-pregnant plasma and then substitute placental serum in the middle of the course of treatment. The other was to substitute non-pregnant plasma for placental serum in the middle of the course of treatment. With both methods there was improvement during therapy with the placental serum and absence of improvement with the non-pregnant plasma.

Discussion. It is known that with many new methods of treatment for rheumatoid arthritis a majority of patients will show an early temporary improvement. With the use of placental serum, however, it must be pointed out that a few weeks are required before any noticeable improvement occurs and the improvement usually continues only as long as semi-weekly injections are maintained. In 25% the interval of injections can be extended to 1 week; in another 25%, it can be discontinued for 3 to 6 months before relapses occur.

Our observations show that treatment must be continued over a long period of time in order to obtain the desired results. It is probable that substances in the placental serum other than ACTH or cortisone are responsible for the clinical improvement, since otherwise we would not expect the 1 to 6 months of apparent clinical remission which were obtained in ¼ of our cases. We feel that our results (reduction of interphalangeal joint swelling, increased joint motion and power, decreased pain, reduction of sedimentation rate) are due to the effect of the placental serum itself. It is to be noted that there were no untoward side effects or toxic manifestations in any of our patients. Two case histories are summarized to illustrate the manner of response to placental serum.

ILLUSTRATIVE CASE REPORTS. CASE 10. Y. L. was a 57-year old white female with a history of rheumatoid arthritis for 7 years. Examination disclosed painful, swollen and fusiform proximal interphalangeal joints in both hands. The sedimentation rate on March 13, 1950, was 31 mm. in 1 hour, and roentgenograms showed a Stage 2 or moderate type of arthritis. The patient was started on placental plasma injections, 10 cc. twice a week. After 4 injections she stated that she felt generally improved and that the pain in her fingers had diminished. Following a total of 12 injections flexion of the fingers increased, swelling receded considerably and she had increased power of the hands. Following 16 injections, she felt so well, and swelling of interphalangeal joints was so minimal, that treatment was discontinued. The sedimentation rate at this time remained the same, but 5 months later it was 20 mm. in one hour. The patient returned on November 9, 1950, after a 6 months' interval, now presenting the same symptoms and findings as previously. Following 3 placental serum injections the pain and swelling decreased and flexion of the fingers improved. The patient received a total of 18 injections and was again discharged in an apparent clinical remission, although the sedimentation rate showed no change. On June 12, 1951, after a 6-month-remission, the patient returned again with complaints and findings similar to those at the first visit, and has again shown decided improvement after 8 injections.

CASE 20. E.C. was a 23-year old colored female with a history of Marie-Strümpell's disease of 5 years' duration. The patient had had continuous severe, crippling low back pain, with pronounced curvature of the spine, causing considerable difficulty in walking. Roentgenograms showed the findings typical of Marie-Strümpell's disease. The sedimentation rate on March 6, 1950, was 40 mm. in 1 hour. The patient was started on placental plasma, 10 cc. twice a week, on March 30, 1950. After 5 injections, the patient noted marked relief of pain, she felt stronger, her appetite improved, and her back deformity diminished especially on walking. The sedimentation rate dropped to 24 mm. in 1 hour

after 5 more injections. Following a total of 16 injections, placental plasma was discontinued since the patient was symptom free and could move about with ease due to lessening of the spinal deformity. The sedimentation rate at this time was 24 mm. in 1 hour. One month later, although the patient was still feeling well, the sedimentation rate rose to 40 mm. in 1 hour. Approximately 3 months after the last injection the patient returned to the clinic presenting many of the original symptoms and findings, including the original deformity of the spine with its limited motion. Nineteen injections of placental serum were given at weekly intervals with the same beneficial results as previously noted. The patient now has another clinical remission which has been maintained except for occasional lapses which respond to only 2 or 3 injections of placental serum. The patient was last seen on July 7, 1951, and was asymptomatic.

Summary. Thirty-three patients with rheumatoid arthritis and 2 cases of Marie-Strümpell's disease have been treated with placental serum during a period of 1½ years. The results have been satisfactory and encouraging.

The technic of obtaining placental serum is described. The serum is easily obtained, is plentiful; costs little, and has no untoward effects.

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CROSS TRANSFUSION. III.
CLINICAL EXPERIENCES WITH 6 CASES*

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RECIPROCAL blood transfer is a procedure which brings about admixture of the blood of 2 individuals so that all substances and particles contained in the blood of one partner will be distributed throughout the blood stream of the other. The internal organs of each individual are then exposed to metabolites contained in the blood and interstitial fluid of both. When organs of one of the partners in a reciprocal blood transfer are not working efficiently, their functions can be taken over by the other partner as long as the circulations of the two bodies are linked. The possible use of a donor body to replace the functions of damaged organs in a patient has been pointed out repeatedly in the medical literature during the past 400 years, and more recently by Nyiri[14], Vecchietti[24], Slagle and Pons[21], and Salisbury[16,17]. We here report our observations in 6 additional cases.

The experimental and therapeutic potentialities of reciprocal blood transfer are vast; it should be possible to readjust all derangements of internal homeostasis, normalize all electrolyte levels, furnish all needed metabolic substances and remove all accumulated wastes. The donor body undertakes the above functions automatically, perfectly, and without the need for the laborious and often inadequate performance and interpretation of numerous laboratory tests. The great possibilities of reciprocal blood transfer are clearly understood by many clinicians and investigators, but until recently this procedure has been used only in isolated instances because of the inadequate and unsatisfactory technical means available for its application.

The methods which can be used for the performance of reciprocal blood transfer are parabiosis, cross circulation, and cross transfusion.

Parabiosis (Greek for "living side by side"), the union of two individuals by a tissue bridge, requires major surgery and is rewarded by a maximum interchange of only 0.6% of the animal's blood volume per minute[12]. Cross circulation achieves a more satisfactory blood transfer through the use of arteries as a source of blood. The blood flow in the paired anastamoses has never yet been measured accurately, the creation of paired vascular anastamoses is a major surgical procedure

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which causes profuse hemorrhages in heparinized individuals, and cannulation of major arteries such as the femoral may lead to occlusive phenomena and to aneurysms. Because of these technical drawbacks it is open to grave doubt whether or not arterial cross circulation methods could attain the status of clinically acceptable procedures in man.

When the venous side of the circulation is used as a source of blood, reciprocal blood transfer is called cross transfusion. It was decided to study the experimental and clinical possibilities of cross transfusion because it can be performed easily, with little trauma to tissues or blood constituents and with accurate measurement and control of the blood flow by means of an instrument and procedure which became available in 1949[16].

Animal experiments have already confirmed the theoretic considerations as to the potential value of cross transfusion in various unrelated conditions. It has been shown that this is an effective means of lowering the levels of nitrogenous waste products in animals with experimental uremia[18]. It can also extend the life span of animals with irreversible renal damage, and it is effective as a therapeutic measure in acute mercury nephrosis. A definite protective effect of cross transfusion has also been demonstrated in dogs which had received lethal doses of irradiation[19].

In human patients numerous cases of reciprocal blood transfer are on record. Duncan, Tocantins, and Cuttle[10] interchanged volumes up to 26,700 cc. between 3 patients with uremia due to cystic renal disease and 3 normal donors. Transitory beneficial effects were observed and the donors were not harmed. The work was discontinued because of the war. Prinzmetal, Friedman, and Rosenthal[15] reported cross transfusions of up to 2,700 cc. between terminal patients, but did not give details about their 4 cases.

Slagle and Pons[21] treated a patient with acute anuria due to mercury by means of cross transfusion of 5,000 cc. by a multiple bottle method. The patient was improved and the donor showed no sign of injury, except for a mild, transitory febrile reaction.

Bierman *et al.* have published reports[2–7] of 7 instances of reciprocal blood transfer. They resorted to cannulation of the femoral arteries after their attempts to apply a cross transfusion method had been unsuccessful. Their papers contain selected hematological and clinical data, and provide significant information about the fate of normal and abnormal leukocytes after transfer to another person.

Wallerstein[26] transferred 9,000 cc. of blood between a child with leukemia and a convict donor. Vacuum bottles were used and the procedure took several days. The patient did not appear improved, but the donor was not harmed.

Satinsky[20] performed a reciprocal transfer of an unknown amount of blood between a child with terminal infectious hepatitis and a donor. A cross circulation method was used which connected arteries to veins by means of plastic tubing. The child died, but the donor was not permanently harmed, although he contracted hepatitis.

Vecchietti[23–25], Vasciaveo[22], and Alfieri[1] have performed a total of 119 cross transfusions between sick patients and healthy donors. A vein-to-vein method was used, which permitted total exchanges of up to 10,000 cc. before the apparatus became obstructed by protein deposits. The procedure proved beneficial in numerous cases of toxemia of pregnancy and of hypertensive and renal disease. Unfavorable

reactions were observed in only 20% of these persons. There were elevations of temperature up to 102°, which started about 24 hours after the procedure and lasted for a day or two. The fever was not accompanied by chills or malaise. There were also a few cases of urticaria. None of the donors or patients sustained any permanent injury. In 3 preliminary cases of our own[17] cross transfusions up to 2,000 cc. were performed without injury to patients or donors.

From the above information it is evident that although earlier workers used methods which were technically not as satisfactory as ours, reciprocal blood transfer has been performed on human persons in many instances.

Our series is made up of patients suffering from a variety of illnesses for which all conventional methods of treatment were not efficacious and for whom cross transfusion was offered and attempted as a treatment of last resort.

Case Reports. CASE 1. J. B., a 42-year old white male, had been a known hypertensive for 5 years, during which time his blood pressure rose to and remained at a level of between 210/160 and 260/210. Symptoms and signs gradually became more severe and consisted principally of headache, vertigo, dyspnea, orthopnea, edema, amblyopia, oliguria, and nocturia. Repeated hospitalizations for treatment with most of the available forms of therapy, including a Smithwick type of sympathectomy in March, 1949, failed to halt the progress of his disease.

He entered a Long Beach hospital December 27, 1949, incapacitated by the severity of his symptoms. On January 14, 1950, there were severe pulmonary edema (confirmed by a chest plate) and eye ground changes classified as Keith-Wagner grade 4.

On January 14, 1950, at 8:20 a.m., the patient received morphine sulfate, 15 mg., and diphenhydramine, 100 mg., subcutaneously. At the same time surgical dissection of the left saphenous vein was begun. At 9:55 the patient, whose weight was about 140 lb., received 200 mg. heparin intravenously, the catheter was inserted, and cross transfusion with the donor was started at 10:00 a.m. at a rate of 8,400 cc. of blood flowing in each direction per hour. The patient tolerated the procedure very well, except for a slight chill which occurred at 11:10 a.m. and subsided after intravenous injection of 150 mg. pentobarbital sodium. Cross transfusion was stopped at 3:30 p.m. when 46,000 cc. blood had been transferred in each direction.

On January 15th, the patient was mentally alert, and the headache, vertigo, dyspnea, orthopnea, and amblyopia had disappeared. Temperature and pulse rate were normal. Fundoscopy showed that the papilledema had disappeared. Auscultation and a chest plate showed no evidence of lung edema. Other than an elevation of temperature to 102.4°, which lasted for only 6 hours, and a slight leukocytosis following the procedure, the patient suffered no ill effects. Between January 14 and February 4, the patient's blood pressure remained consistently at lower values than before, and reached maximum high values of 250/130 on only 2 occasions. The patient continued to feel well and became ambulatory around the hospital without recurrence of symptoms until February 1, 1950, when there was moderate edema of the scrotum. During the evening hours of February 2, 1950, he suddenly developed severe generalized edema, with Kussmaul-type respiration and stupor. He expired February 4, 1950. Autopsy was denied.

COMMENT. There was no autopsy but it is safe to say that this patient was suffering from acute renal insufficiency associated with severe hypertension. Cross transfusion caused a striking improvement which continued for 15 days. This improvement was characterized by the improved subjective state of the patient, disappearance of papilledema, pulmonary edema, dyspnea and headache, the lowered blood pressure levels, and the lowered blood creatinine. Signs of possibly adverse reactions to the procedure consisted only in a temporary delayed elevation of temperature and a transitory leukocytosis which started during the procedure and subsided within one day.

DONOR 1. D. R., a 22-year old white male, weighing 220 lbs., requested to be a donor for

TABLE 1.—LABORATORY DATA CONCERNING THE PATIENT, J. B., IN CASE 1

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Other Data*
12/27/49	Sp.g. 1.012, pH 7.4 Albumin 3+, 8–10 WBC 6–10 RBC/hpf		Creat. 3.8	B.P. 250/180
1/2/50			Creat. 6.95 NPN 90.5 BUN 53.4	B.P. 240/180
1/7/50		Hb. 10.9 gm. RBC 3,150,000 WBC 9,800 (p. 86, l. 32, eos. 2)	Creat. 11.2 NPN 89 Chlorides 442	B.P. 250/175
1/9/50			Calcium 8.5 Phosphorus 4.5	B.P. 230/180
1/14/50 8:00 A.M., before cross transfusion		Hb. 8.6 gm. RBC 2,890,000 WBC 8,400 (p. 84, l. 15, eos. 1)	Creat. 12.9	B.P. 220/175
1/14/50 12M, 16,800 cc. blood exchanged		Hb. 11.2 gm. RBC 3,900,000 WBC 9,400 (p. 87, l. 11, eos. 2)	Creat. 8.7	B.P. 180/140
1/14/50 2:15 P.M., 35,000 cc. blood exchanged		Hb 11.5 gm. RBC 3,100,000 WBC 17,200 (p. 100%)	Creat. 7.8	B.P. 190/150
1/14/50 3:30 P.M., 46,000 cc. blood exchanged		Hb 10.21 gm. RBC 3,250,000 WBC 25,300 (p. 98, l. 2)	Creat. 6.3	B.P. 190/150
1/15/50	pH 7.5, sp.g. 1.015 Alb. trace, WBC few, RBC many, casts not seen	Hb. 11.5 gm. RBC 3,570,000 WBC 10,000 (p. 90, l. 10)	Creat. 7.6 BUN 76 uric acid 8.2	B.P. 180/120
1/18/50	pH 7.5, sp.g. 1.010 Alb. 2+, WBC many, RBC many		Creat. 10.9	B.P. 180/100
1/20/50	pH 8.0, sp.g. 1.011 Alb. 4+, WBC solid field		Creat. 10.9	B.P. 170/90
1/23/50		Hb 10.5 gm. RBC 3,000,000 WBC 8,400 (p. 80, l. 20)	Creat. 13.9 BUN 94.8 NPN 124 Chlorides 393 Plasma alb.: globulin 4.3/1.5 (gm.)	B.P. 180/140
1/25/50		Hb. 11.8 gm. RBC 3,500,000 WBC 10,000 (p. 65, l. 35)	Creat. 12.9	B.P. 180/110
1/26/50	pH 4.0, alb. 3+ WBC many			B.P. 175/90
1/28/50			Creat. 13.0 NPN 135 Chlorides 358	B.P. 180/140
1/31/50			Chlorides 345	B.P. 160/120
2/1/50			Creat. 13.5 BUN 51 Chlorides 363 CO_2 comb. 32.8 vol.%	B.P. 160/110
2/4/50			Creat. 13.6 Chlorides 303	B.P. 150/100

B.P. = blood pressure
p. = polymorphs
l. = lymphocytes
eos. = eosinophils
Hb. = hemoglobin
Alb. = albumin
Creat. = creatinine
Sp.g. = specific gravity
BUN = blood urea nitrogen
WBC = white blood cells
RBC = red blood cells
NPN = non-protein nitrogen

J. B. in the cross transfusion procedure and stated that he had always been in good health. Physical examination did not disclose abnormalities.

On January 14, 1950, he received morphine sulfate, 30 mg., dramamine, 50 mg., and diphenhydramine, 50 mg., subcutaneously, and 300 mg. heparin intravenously. Cross transfusion was performed as above.

During the procedure the donor's blood pressure gradually rose from 130/80 to a high of 170/70 at 12:25 p.m., when 20,000 cc. had been transferred. The pressure then started to fall and became stabilized at 105/65 at the end of the cross transfusion. At 11:00 a.m. (8,400 cc. exchange) there was nausea and vomiting, and the patient had a chill. Intravenous fluids were then started, and he also received 150 mg. sodium pentobarbital intravenously. On 2 more occasions during the procedure he received an additional 50 mg. pentobarbital. Auscultation at 11:35 revealed a slight diffuse wheezing, which was attributed to bronchial constriction, and disappeared promptly after 0.2 cc. of 0.1% epinephrin had been given subcutaneously. The rest of the cross transfusion was uneventful with the patient sleeping comfortably until 2:00 p.m., when he awakened. He had received 1,000 cc. of 5% glucose and 1,000 cc. of sodium lactate solution intravenously during the cross

TABLE 2.—LABORATORY DATA CONCERNING D. R., DONOR IN CASE 1

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Treatment*	*Observations*
1/14/50 8:20 A.M.	pH 6.5 sp.g. 1.020 alb. 1+ WBC 1–2/hpf RBC none			Morph. sulf. 30 mg. Dramamine 50 mg. Diphenhydramine 50 mg.	
9:55 A.M.				Heparin 300 mg. (1.3 Mg./lb.)	B.P. 130/80
11:00 A.M. 8,400 cc. exchanged	pH 4.5 S.G. 1.012 alb. 2+ RBC 20–24/hpf			Pentobarb. 150 mg. i.v.; i.v. fluids started	nausea, chill
12:25 P.M. 20,000 cc. exchanged	pH 4.0 S.G. 1.014 alb. 2+ RBC 150–200 casts 1–2 1 pf	Hb. 12.2 gm. RBC 4,370,000 WBC 7,600 (p. 98, l. 16)	Creat. 4.3	Epinephrin 0.2 cc. 0.1%	bronchial wheezes B.P. 170/70
2:15 P.M.			Creat. 4.6		B.P. 105/65
3:30 P.M. 46,000 cc. exchanged	pH 4.0 sp.g. 1.014 alb. 2+ RBC 200–300 casts 3–6/1 pf	Hb. 11.0 gm. RBC 3,440,000 WBC 15,400 (p. 97, l. 3)	Creat. 3.9		B.P. 105/65
1/15/50	s.g. 1.015 2–3 WBC/hpf pH 5.6	Hb. 13.2 gm. RBC 4,600,000 WBC 7,200 (86 p., 7 l., 3 mono., 2 eos.)	Creat. 1.3 Sed. R. 6 mm/60′ Blood culture normal	Aureomycin, 6.0 gm. Streptomycin, 3.0 gm. Penicillin, 1,000,000 U	B.P. 110/70 T. to 103°
1/16/50	normal	CBC normal	Thymol turb. 3 Ict. ind. 10 Ceph.-choles. normal PSP normal	As above	Chest plate, E.C.G. normal T. to 104°
1/17/50				As above	T. to 101°
1/18/50	normal	CBC normal	Creat. 0.9		T. normal B.P. 110/7
1/28/50		Hb. 12.0 gm. RBC 4,000,000 WBC 5,800			
9/23/50	normal	normal			B.P. 115/80 Passed pilot exam.

mono. = monocytes
CBC = complete blood count
ECG = electrocardiogram
i.v. = intravenously
Pentobarb. = pentobarbital
Ict. ind. = icterus index
PSP = phenolsulfonphthalein excretion
For other explanations see Table 1

transfusion. His temperature and pulse rates during the procedure were normal.

After termination of the procedure the patient insisted that he be permitted to leave the hospital in order to keep a social engagement. He was readmitted to a hospital at 11:00 p.m. the same evening because of oozing from a subcutaneous vein.

At 10:10 a.m. on January 15, there was a chill and the temperature was 103.6°. Treatment was instituted with aureomycin, 6.0 gm. per day, streptomycin, 3.0 gm. per day, penicillin, 1,000,000 units per day. Temperatures up to 104° were noted until January 17th when the temperature became normal. Except for 3 severe chills, the patient did not feel ill during the stay in the hospital. He was discharged January 20, 1950, returned to his work as a freight handler on January 24, and has subsequently remained well. In October, 1950, he was accepted for pilot training.

TABLE 3.—LABORATORY DATA CONCERNING THE DONOR, T. R., IN CASE 2

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Treatment*	*Observations*
3/17/50 1:30 A.M.				Benadryl, 100 mg. Dramamine, 100 mg. $NaHCO_3$, 100 mg. Nembutal, 200 mg. Heparin, 150 mg.	B.P. 110/60
6:00 A.M.	60–80 RBC 8–10 WBC/hpf Alb. 2+ No casts				
11:30 A.M. 45,000 cc. (?) exchanges					B.P. 110/60 Comfortable
7:00 P.M.	70–90 RBC 8–10 WBC/hpf Alb. 2+				
3/18/50	50–60 RBC 10–20 WBC/hpf No casts alb. 0	Hb. 12.9 gm. RBC 3,750,000 WBC 12,600 (p. 86, l. 11, eos. 3)	Creat. 1.0 Blood cult. neg.	Aspirin, gr. x	T. to 104°
3/19/50	12–20 RBC 4–5 WBC/hpf Numerous gran. casts	Hb. 12.5 gm. RBC 3,660,000 WBC 12,900 (p. 80, l. 18, eos. 2)	Creat. clearance 78 cc./min.	Aureomycin, 2.0 gm. Aspirin, gr. x	T. to 103.8°
3/20/50	Normal			Penicillin, 1,000,000 u Aureomycin, 2.0 gm. Aspirin, gr. x	T. to 102°
3/22/50					T. normal
5/29/50	Addis count norma	Hb. 15.5 gm. RBC 5,000,000 WBC 6,000 (p. 55, l. 45) Platelets 150,000	NPN 43 Ict. ind., 4.0 Thymol turb. 4 Creat. clear. 122 cc.		

For explanation of abbreviations see Tables 1 and 2

COMMENT. This donor tolerated the cross transfusion procedure well and seemed to take over the homeostatic functions effectively. Blood counts show that complete mixing of the blood of the donor and patient did occur. The blood creatinine levels are evidence that the donor was actually excreting creatinine at a higher rate than he was receiving it from the patient. The fall of the urine pH to 4.0 indicates that the donor excreted large amounts of fixed acid radicals which presumably came from the patient. Except for one episode of vomiting, chill, and transitory bronchospasm which promptly yielded to treatment, there

was no clinical evidence of unfavorable reaction during the procedure. However, the procedure was discontinued at 3:30 because of the increasing appearance of erythrocytes and granular casts in the donor's urine. Following the cross transfusion the donor felt clinically well but developed a severe febrile reaction which began 24 hours after the start of the cross transfusion procedure and lasted for 3 days. All laboratory tests had returned to normal within 24 hours of the cross transfusion. A reason for the febrile reaction was not discovered and the donor has since remained in good health.

It seems worthy of note that the patient's blood pressure fell and the donor's blood pressure rose during the cross transfusion procedure.

The donor stated that he would undergo the procedure again if it were necessary to help a close friend or relative.

CASE 2. R. S., 38-year old colored male, was admitted to the hospital March 14, 1950, complaining of nausea and of intense right upper quadrant abdominal pain of 2 days' duration. There was a history of many years of alcoholism and of repeated Neisserian infection 8 years before. His abdomen was markedly distended by ascites. The smooth, hard liver edge was felt 4 cm. below the costal margin. Blood pressure varied between 110/70 and 190/100. Eyegrounds showed changes classified as Keith-Wagner III. The patient vomited frequently while conscious and appeared gravely ill.

At 10:00 a.m., March 16th, he became comatose. A diagnosis of hepatorenal syndrome secondary to hepatic cirrhosis was proposed. The patient's blood pressure had fallen to 80/60 at 12:00 noon and remained at shock levels during the rest of the day. After he had gone into coma, urine was not recoverable by catherization. Cross transfusion was started at 1:00 a.m., March 17th. At this time the patient's blood pressure was unobtainable and it was the opinion of the attending physicians that his continued survival was a matter of minutes. Cross transfusion was continued until 11:30 a.m., when a total of 45,000 cc. had been transferred in each direction. During the cross transfusion the patient remained in coma, but his blood pressure gradually rose to 130/110 at 7:00 a.m. He came out of the profound state of shock and assumed a position of opisthotonus which was interpreted as caused by decerebrate rigidity due to the prolonged cerebral anoxia. During the remainder of March 17th and until his death at 4:30 a.m., March 18th, the patient remained in opisthotonus and coma. Following the cross transfusion several hundred cubic centimeters of urine were obtained by catherization.

As the intravenous catheter was withdrawn, it was discovered that the delivery tip had been bent back beyond the withdrawal opening, creating a partially closed circuit. Autopsy showed extensive primary carcinoma of the liver, confined to the subdiaphragmatic portion, and also acute nephropathy with intratubular hemorrhage.

COMMENT. An erroneous diagnosis was made in this patient. The cross transfusion procedure was not as successful as it might have been, because of faulty insertion of the catheter and the preexisting anoxic cerebral damage. It is worthy of note that the profound shock of this moribund patient was reversed, even though the blood volume was not expanded.

DONOR 2. T. R., a 29-year old colored female, requested to be the donor in a cross transfusion with R. S. She stated that she had always been in excellent health. Cross transfusion with R. S. was carried out on March 17th as described above. During the cross transfusion, the donor was comfortable and only complained occasionally of a backache, due to her uncomfortable position in bed. Her blood pressure was maintained at 110/60, and her pulse rate and temperature were normal.

Following the cross transfusion the donor exhibited temperatures spiking to 104° on March 18th, 19th, and 20th, but could not understand why she was kept in the hospital because she did not feel ill.

She was discharged from the hospital March 24, 1950, and returned to work April 1st. She has remained well since and has not shown signs of abnormality in follow-up studies.

COMMENT. Because of a technical error in this case the actual volume of blood transferred from the patient to

the donor is not known, but it must have been considerable. Administration to the donor of a large amount of blood from a patient with primary carcinoma of the liver was well tolerated. There was a marked, transitory febrile reaction in the donor, but recovery occurred promptly and was complete. She stated that she would undergo the procedure again if it were necessary to help a close friend or relative.

CASE 3. M. D. W., a 31-year old white female hospital attendant, was admitted to the hospital on February 15, 1950. She had suffered from scarlet fever at 1 year of age, had a tonsillectomy at age 10, and was "seriously ill" for a period of 1 week in 1947 without consulting a physician. She is married and had a normal pregnancy in 1943. The child is living and well. In the spring of 1949 she had been treated for overweight (200 lbs.) and hypertension of 170/110 was discovered at that time. With amphetamine and limitation of dietary intake her weight was reduced to 140 lbs., and her blood pressure fell to normal levels.

She suffered a severe "cold" in January, 1950, and noted swollen ankles on February 3, 1950. On admission February 15, 1950, she weighed 175 lbs.; her abdominal, gluteal, presacral, and crural subcutaneous tissues were distended with edema; and she was dyspneic. Plasma albumin was 1.9%, plasma globulin 1.7%. Blood cholesterol was 500 mg. The fundi were normal, blood pressure was 110/65. Further laboratory findings are summarized in Table 5. A diagnosis of nephrotic syndrome due to chronic glomerulonephritis was made. Her weight remained stationary around 175 lbs. in spite of a salt poor diet

TABLE 4.—LABORATORY WORK CONCERNING M. D. W., PATIENT IN CASE NO. 3

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Medication*	*Observation*
3/10/50	13 gm. protein/24 hr. 5–6 WBC/hpf	Hb. 18.0 gm. RBC 5,020,000 WBC 14,800	A/G 1.9/1.7 Creat. 0.85 Urea N 8.0		B.P. 110/65 Wt. 176 lb.
3/13/50	20 gm. protein/24 hr.	WBC 8,900 (p. 53, l. 44)	PSP 65% Creat. clear. 78 cc. Choles. 500		Wt. 175 lb.
3/23/50 25,000 cc. cross trans.	loaded with WBC		A/G after cross trans. 3.1/2.7 (gm.) Creat. clear. 100 cc./min.	Heparin 150 mg. Penicillin, 1,000,000 u Streptomycin, 2.0 gm.	T. to 99.8° Wt. 175½ lb.
3/24/50	Alb. 4+ 5–9 WBC 0–1 RBC/hpf Occ. casts	Hb. 12.7 RBC 5,000,000 WBC 7,500 (p. 75, l. 21, eos. 3)		Penicillin, 1,000,000 u Streptomycin, 2 gm.	T. to 101.4° Wt. 173 lb.
3/25/50	4.0 protein/24 hr.	Hb. 14.6 WBC 6,250 (p. 80, l. 17, eos. 3)			T. to 101° Wt. 171 lb.
3/30/50	9.7 gm. protein/24 hr.	Hb. 14.6 RBC 4,700,000 WBC 7,550 (p. 58, l. 32, eos. 3)	A/G 1.5/3.3 (gm.) Creat. 1.0		T. normal B.P. 115/65 Wt. 157 lb.
5/9/50	1.5 gm. protein/24 hr.				Wt. 136 lb.
5/24/50	0.3 gm. protein/24 hr.	Hb. 16.2 RBC 4,700,000 WBC 14,400 (p. 74, l. 22, eos. 1)	A/G 4.4/2.9 (gm.) Creat. clear. 56 cc. Creat. 0.89 mg.		dental infection Wt. 138 lb.
7/17/50	protein 0	Hb. 15.7 RBC 4,880,000 WBC 10,500 platelets 356,000	NPN 26.4 BUN 12.4 Ict. ind. 9.5		Wt. 137 lb.

A/G = albumin-globulin ratio
For other explanations of abbreviations see Tables 1 and 2

containing 50 gm. of protein per day. She remained in bed for 1 month without change and her prognosis appeared grave.

Cross transfusion was performed in the usual manner on March 23, 1950. Following cross transfusion she felt essentially as before except for a temperature rise to 101.6° on March 24th, and to 102° on March 25th. Temperatures and pulse rates were normal thereafter.

Immediately after the cross transfusion a copious diuresis began. For about 3 weeks she passed more than 4 liters of urine daily. After 3 weeks her weight had fallen to 138 lb.; she became ambulatory and felt well. On May 15th she returned to work and has felt well since.

COMMENT. Immediately after 1 cross transfusion of 25,000 cc. a striking improvement began in this patient with the nephrotic syndrome. The patient has since remained well and all laboratory studies are normal. Although spontaneous cures of the degenerative stage of chronic glomerulonephritis are known to occur in about 2% of the afflicted patients, the course before treatment and the time relationships leave little doubt that improvement in this patient is to be attributed to the cross transfusion procedure.

TABLE 5.—LABORATORY DATA CONCERNING THE DONOR, L. V., IN CASE 3

Date	*Urine*	*Blood Morphology*	*Blood Analysis*	*Medication*	*Observations*
3/19/60	No abnormal findings	Hb. 12.9 gm. RBC 3,900,000	Creat. clear. 63 PSP 53%/60′ Th. Turb. 4 Creat. 1.0		
3/23/50 1:20 P.M. 6,000 cc. exchanged			Creat. clear. 100 cc./min.	100 mg. diphenhydramine ½ cc. 0.1% epinephrine 1 mg. heparin/lb. (120 mg.)	urticaria
2:10 P.M.				300 mg. sod. amytal IV	B.P. 74/60
2:20 P.M.	2–3 granular casts 3–15 WBC 2–7 RBC/hpf		Creat. clear 125 cc./min.	5 mg. neosynephrin 300 cc. plasma started 1000 cc. 5% glucose 500 cc. sod. lactate started	B.P. 90/65
3/24/50	15–20 WBC 3–7 RBC/hpf Occ. Hb. casts	Hb. 10.6 gm. RBC 3,830,000 WBC 4,900		Penicillin 600,000 u Streptomycin 1.0 gm. Chloromycetin 1.0 gm. Aspirin gr. x Diphenhydramine 100	T. to 101° B.P. low of 80/60
3/25/50	Alb. trace 1–2 WBC/hpf	Hb. 11.7 gm. RBC 4,300,000 WBC 6,100 (p. 79, l. 19, eos. 2)	A/G = 3.0/2.2	Streptomycin 1.0 gm. Chloromycetin 1.0 gm.	T. to 103.2°
3/26/50				Chloromycetin 1.0 gm. Aspirin gr. x	T. to 104.4°
3/27/50			Sed. Rate 6 mm./60′	Chloromycetin 1.0 gm.	T. to 100.6°
3/28/50			A/G = 4.2/3.6		T. to 99°
5/22/50	Addis count normal	Hb. 15.3 gm. RBC 5,000,000 WBC 6,500 (p. 68, l. 32)	NPN 40.6 Ict. ind. 12 80% prothrombin time		
6/12/50	normal	CBC normal platelets 186,000	NPN 32 A/G = 4.6/3.3 Ict. ind. 10 Th. turb. 8 Bromsulf. 15% retained		

For explanation of abbreviations see Tables 1, 2, and 4

Undesirable side reactions were so slight in this patient as to be almost unnoticeable. They consisted only in a moderate elevation of temperature occurring 2 or 3 days after cross transfusion.

Donor 3. L. V., a 41-year old married white saleswoman, was hospitalized for investigation March 19, 1950. The past history was essentially negative except for the usual childhood diseases, 2 normal pregnancies 20 and 21 years before, and 1 dilatation and curettage. Physical examination did not disclose abnormalities, but the donor appeared tense, nervous, and irritable, and complained of frequent occipital headaches. On March 23, 1950, at 12:45 cross transfusion was started and terminated at 3:20 after 25,000 cc. had been exchanged in each direction. Following the cross transfusion the donor continued to receive sedatives, antihistaminics, and ephedrin, and consequently felt tired and weak. She was discharged March 28th, and returned to work April 5th. Since then she has continued to work, feels well, and laboratory studies have yielded normal findings.

Comment. This donor recovered completely from the cross transfusion procedure, and no abnormal clinical or laboratory findings were noted 1 week after the cross transfusion. During the procedure itself, there was a marked urticarial reaction and after administration of sodium amytal intravenously the blood pressure fell to 74/60, but promptly returned to normal levels after administration of neosynephrin. The creatinine clearance was depressed during the procedure, probably because of the lowered blood pressure. Urinalysis showed increased numbers of red cells during and for several days after cross transfusion. A marked febrile reaction started 24 hours after the transfusion and lasted for 3 days. She stated that she would gladly undergo the procedure again if called upon.

Case 4. C. L., a 39-year old white male weighing 147 lb., had not worked for several years. He was suffering from periodic attacks of pain attributed to gout and had been told he had hypertension. In December, 1949, he consulted a physician because of backache, "puffy face and puffy eyes." Albuminuria was discovered at that time. Between December, 1949, and March 14, 1950, when he was seen in the clinic, he had gained 10 lbs., and during the intervening time he had become more tired, was suffering from intense headaches most of the time, and had moderate dyspnea. On admission to the hospital April 7, 1950, he appeared acutely ill, his face was edematous, there was some orthopnea and dyspnea, and his skin appeared pale and pasty. A diagnosis of chronic glomerulonephritis was made.

Cross transfusion was started April 11, 1950, at 9:55 a.m. and stopped at 2:00 p.m., when 51,200 cc. had been transferred in each direction. During the cross transfusion the patient felt well, his temperature and respiration remained normal, and his pulse rate varied between 72 and 94. However, urine was not recovered from the catheter between 11:20 a.m. and 4:00 p.m., and concern was felt about his temporary anuria, which was the reason for stopping the procedure.

Following the cross transfusion, the patient's headache disappeared and did not return, he felt stronger and more alert, and the face and eyes lost their "puffy" look. For 5 days after the cross transfusion the temperature was somewhat elevated, with a maximum of 101.4° on April 16th. There was a thrombophlebitis in the right calf, with swelling and tenderness, and on April 20th the temperature rose again to 100.2°. He was discharged from the hospital April 25th.

On May 9 the patient returned to the outpatient clinic stating that he had a severe backache. He was rehospitalized May 11th because he had fainted at his home. On admission he appeared ill, complained of severe pains in his back and extremities, and exhibited diffuse, tender, nodular subcutaneous infiltrations all over his body. Fever was first noted May 12th and continued until his death May 23rd. His course in the hospital was characterized by diffuse, severe pain and tenderness, progressive anemia and leukopenia, jaundice (up to icterus index 44), and diffuse intracutaneous hemorrhages, which became more and more confluent.

Autopsy disclosed peculiar nodular formations scattered diffusely throughout the subcutaneous tissues, the gastrointestinal tract, and other organs. The kidneys showed the typical picture of chronic glomerulonephritis. The bone marrow was scanty and presented a picture of aplastic anemia. The nodular formations were caused by bacterial colonies,

TABLE 6.—LABORATORY DATA CONCERNING C. L., PATIENT IN CASE 4

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Treatment*	*Observation*
3/21/50	4.0 gm. protein/24 hr. many granular casts		Creat. 5.3 BUN 50 A/G 4.7/3.4 (gm.)		
3/30/50	3.3 gm. protein 500,000 granular casts/24 hr. 7,000,000 RBC 2,000,000 WBC/24 hr.				
4/7/50		Hb. 17.0 gm. RBC 5,500,000 WBC 8,100 (p. 62, l. 22, m. 15, e. 1)	Creat. 3.2 Uric acid 5.8 Creat. clear. 24 cc. PSP 75%	Colchicine 7 mg. 1.5 mg. o.d.	B.P. 200/140
4/11/50 9:55 A.M.			A/G 4.7/3.3 Cholesterol 300	Premedication: Nembutal, gr. 3 Sod. bicarb. 10 gm. Pyramidon gr. x Benadryl 100 mg. Dramamine 100 mg.	B.P. 180/130
11:00 A.M.					B.P. 140/115
2:00 P.M. 51,200 cc. blood exchanged	urine not recoverable during procedure		A/G 4.0/3.0 Creat. 1.2 BUN 19 Uric acid 3.8	Aminophyllin Plasma, 5% glucose i.v.	B.P. 90/60 after aminophyllin
4:00 P.M.	300 cc. urine 10–15 RBC 1–2 WBC/hpf				B.P. 130/80
4/12/50				Penicillin 600,000 U Demerol 150 mg. Neosynephrin 20 mg.	T. to 99.4°
4/13/50			Prothrombin 31%	Penicillin 600,000 U Nembutal Demerol	T. to 99.6°
4/14/50				Penicillin 600,000 U	T. to 100.8°
4/15/50				Penicillin 600,000 U Demerol Empirin	T. to 101.2°
4/16/50			Creat. 4.0 Creat. clear 27 cc.	Penicillin Empirin	T. to 101.4°
4/17/50				Penicillin Empirin	T. to 100.2°
4/25/50	8.0 gm. protein 200,000 casts 3,000,000 WBC 2,000,000 RBC/24 hr.	Hb. 11.5 gm. RBC 3,360,000	PSP 20%	Colchine 5 mg.	T. normal
5/9/50					Rash Myalgia
5/11–16/50	408,000,000 RBC 32,000,000 WBC Numerous RBC casts/24 hr.	Hb. 7.3 gm. RBC 1,900,000 WBC 600 (p. 1, l. 99) Platelets 24,000	BUN 32 Creat. 4.2 Prothrombin 35% PSP 19%	Transfusion Benadryl Nembutal Aureomycin 2.8 gm.	Fainting spell B.P. 110/90 Bone marrow scanty Rash T. to 104°
5/17–23/50	As above	Hb. 14.9 gm. RBC 4,900,000 WBC 150 Retics 0.5% Platelets 12,000	Ict. ind. to 44 Creat. 4.5 BUN 72	Aureomycin 2.5 gm. Transfusion	T. to 104°

Retics = reticulocytes
For other abbreviations see Tables 1 and 2

which had provoked a granulomatous reaction, and death was clearly due to the overwhelming infection, in the opinion of several pathologists.

COMMENT. The cross transfusion procedure in this case was effective but was complicated by transitory anuria. After the cross transfusion this patient felt remarkably improved, although the blood creatinine rapidly returned to the original level. There was a moderate febrile reaction after the procedure and thrombophlebitis developed in the right calf. The patient's blood counts were not followed as they should have been. The patient also did not receive adequate antibiotic therapy. The diagnosis of gout appears poorly substantiated by available blood uric acid levels but was clinically typical. As is evident from widely disseminated granulomata, the patient's massive infection, which was the immediate cause of death, preceded the second admission to the hospital. It is not possible to say from the available data whether the infection was caused by existing agranulocytosis or whether the bone marrow was injured by the existence of infection. The infection probably became generalized as a consequence of inadequate treatment of thrombophlebitis. In view of the similar picture in Case 6, the question arises whether cross transfusion itself may have contributed to the bone marrow injury.

DONOR 4. A. S., a 47-year old white married woman, entered the hospital April 9, 1950. Her past history was essentially normal, except for an attack of "pain" in the left foot 1 year ago. On April 11 cross transfusion was performed as described above. The donor did not complain during the transfusion and appeared very comfortable. Following the cross transfusion she remained completely well and did not exhibit abnormalities.

COMMENT. This donor functioned perfectly in cross transfusion and there was no adverse reaction to the procedure.

CASE 5. V. C., a 67-year old man, had been followed at the clinic since 1945 because of a peptic ulcer which led to his hospitalization on 3 occasions. His last admission was in January, 1950, and was caused by massive hemorrhage from the gastrointestinal tract. There was also a finding of glycosuria in 1949, which was not present in further examination thereafter.

Albuminuria and hypertension had been noted since 1947. On April 19, 1950, the blood pressure was 200/140 and the blood creatinine was 6.0 mg.

Cross transfusion was started April 25, 1950, at 10:10 a.m. and stopped at 2:00 p.m., when 50,200 cc. had been transferred in each direction. The patient tolerated the procedure well and rested comfortably in bed. Following the cross transfusion he remained well except for a slight fever, lasting 3 days, and no further treatment was administered, except tincture of hyoscine and a salt-poor, protein-poor ulcer diet. He was discharged from the hospital May 2nd and has since been seen several times, when he was feeling well.

COMMENT. Cross transfusion of 50,200 cc. was performed in a patient with the diagnosis of peptic ulcer and of azotemia secondary to renal insufficiency due to chronic glomerulonephritis. The procedure was tolerated well and resulted in a marked lowering of the blood creatinine, which persisted for a few days. A mild and transitory febrile reaction occurred in this patient. The patient was clinically improved and has remained asymptomatic for one year.

DONOR 5. I. C., is a 30-year old, unmarried secretary whose previous history and physical examination were not remarkable. Cross transfusion was performed as described above. She was discharged May 1st, returned to work May 3rd, and has been well since then.

COMMENT. This woman was the donor for a cross transfusion of 50,200 cc. of blood with her father, who was suffering from azotemia and hypertension due to chronic glomerulonephritis. Except for a moderate febrile reaction, which lasted 4 days, she did not appear

to be harmed by the procedure in any way.

CASE 6. R. L., an 11-year old boy, was admitted to the hospital April 10, 1950. Except for poorly defined information about the usual childhood diseases and for a head injury in 1949, he had been in good health until March 31, 1950. He then noted some "pimples or fleabites" on his abdomen and he also noted swelling of his feet. The edema gradually increased and albuminuria was discovered, which led to his hospitalization. Lesions present were massive pitting edema of the lower extremities and dependent parts, shotty cervical lymph nodes, and numerous discrete macular lesions 1 to 2 mm. in diameter over the chest and abdomen. There was also massive proteinuria. During his stay in the hospital his weight had increased from a normal 70 lbs. to a maximum of 92 lbs. A number of therapeutic measures such as intravenous sucrose and salt and protein restriction had been tried without success. On May 1st he appeared dyspneic and fine crepitant rales were noted over both lower lung fields by the attending pediatrician. His temperature was normal. Blood pressure was 110/80.

On May 2, 1950, cross transfusion was performed without premedication except for 80 mg. of heparin. Between 9:15 a.m. and 12:00 noon 25,100 cc. of blood were transferred in each direction. The patient tolerated the procedure very well and received no additional medication except atropine, gr. 1/200, which effectively relieved nausea. He vomited once during the procedure. His blood pressure rose from an initial 128/80 to 150/110 at the end.

Following the cross transfusion there was a febrile reaction, lasting 3 days, with maximum temperature of 103°. The proteinuria was unchanged. Clinically, the boy was improved and there had been loss of edema and reduction of body weight to 82 lbs. The patient was then lost from observation, but another physician has reported him improved clinically and from the laboratory point of view.

DONOR 6. S. L., a 40-year old workman, was the father of R. L. He had in the past suffered from frequent colds and from a chronic postnasal discharge which was attributed to sinusitis. Physical examination was normal except for a questionable Rumpel-Leede (capillary fragility) test, slightly accentuated respiratory sounds with occasional diffuse wheezes, reddened pharynx, and the fact that there was almost complete absence of hair, except on his legs. The atrichia was said to have been present for many years.

On May 2nd, cross transfusion was performed as described above. The donor tolerated the procedure without any difficulty and was comfortable throughout, except for the appearance of diffusely distributed urticarial wheals at 10:15 after 7,600 cc. had been transferred. Urticaria promptly disappeared after injection of 1.0 cc. of 0.1% epinephrin, 25 mg. ephedrin sulfate, and 20 mg. diphenhydramine. His blood pressure throughout the procedure varied between 117 to 155/70 to 90.

In contrast to all other patients and donors in previous cross transfusions, this donor began to feel very uncomfortable shortly after termination of the procedure. He complained of severe malaise, fatigue, a burning sensation especially severe over the skin of the lower extremities, and diffuse abdominal muscular tenderness. There were also chills and some nausea. A soft spleen was palpated 3 cm. below the costal border, where it remained. On May 6 and 7, a morbilliform rash was noted on his trunk and a confluent macular rash was present in the right axillary region. These eruptions disappeared on May 9th. On May 10th, many diffuse, fine, reddish-gray, "dusty" eruptions were noticed and these continued until May 14th. His condition did not cause undue concern until May 9th, because in preceding cases of cross transfusion the donors had exhibited febrile reactions which eventually subsided. It will be noted (Table 7) that up to May 9th there were no laboratory findings which showed a trend toward further abnormality.

His symptoms of malaise, fatigue and tenderness did not improve and the development of a sensitivity reaction was suspected. Muscle biopsy, May 9th, did not show any abnormality. Jaundice was noted on May 10th. In spite of the negative biopsy, a sensitivity reaction was thought to have occurred and the patient was given 200 mg. of cortisone in the evening hours of May 11th. On May 12th his temperature was normal and he received another 200 mg. cortisone. Symptomatically he was not improved. On May 13th, the temperature mounted to 102°, in spite of another 100 mg. cortisone. During the early morning hours of May 15th he expired.

Up to the time of his death there was only evidence of hepatic insufficiency, mild to moderate renal damage, and depression of the bone marrow. The liver and spleen were somewhat enlarged, and the peculiar eruption and the severe malaise, discomfort and diffuse muscular soreness of the patient were present.

Autopsy showed acute, severe edema of the brain, the liver, and the kidneys. Micro-

scopically, there were atrophy of bone marrow with hyperplasia of reticuloendothelial cells, central necroses of liver and focal necroses of spleen, minimal lower nephron nephrosis, and edema of brain and lungs.

COMMENT. This donor who, before cross transfusion, exhibited slight abnormalities, died 14 days after a cross transfusion procedure. The clinical course was one of severe malaise, fatigue, and muscular and cutaneous pain and tenderness. During the last 4 days there were moderate jaundice, mild azotemia, and evidence of bone marrow depression. At autopsy none of the internal organs seemed incapable of

TABLE 7.—DATA CONCERNING S. L., DONOR IN CASE 6

Date	*Urine*	*Blood Morphology*	*Blood Analysis (mg./100 cc.)*	*Treatment*	*Observation*
4/30/50	Alb. 0 Sp.g. 1.018 Sed. occ. WBC	Hb. 17.0 gm. RBC 5,580,000 WBC 8,300 (p. 74, l. 21, mono. 4, eos. 1) Platelets 280,000	NPN 35 Creatinine 1 A/G = 4.6/2.6 (gm.) Prothrombin 50% PSP 66%	Chloromycetin, 1.0 gm. Codeine, gr. ½	T. to 100° B.P 120/70
5/1/50	21,000,000 RBC 2,000,000 WBC/24 hr. 1 granular cast Alb. trace				T. to 99.4°
5/2/50 Cross transfusion 25,000 cc. exchanged	Alb. 0 4–8 WBC/hpf			Neosynephrine, 2.5 mg. Chloromycetin, 1.0 Penicillin 300,000 u Heparin, 150 mg. Benadryl, 50 mg.	T. to 101°
5/3/50	Alb. 0 Sp.g. 1.017 0–1 RBC/hpf 2–5 WBC/hpf	WBC 8,800 (p. 84, l. 9, mono. 5, eos. 2)		Empirin Codeine Penicillin	T. to 102.5°
5/4/50	Same		BUN 12 Creat. 1.2 A/G = 3.4/2.3 (gm.)	Empirin Codeine Aspirin Penicillin	T. to 104°
5/5/50		Hb. 14.9 gm. RBC 4,350,000 WBC 7,300 (p. 86, l. 11, eos. 3) Platelets 86,000	SR 40 mm/60′ Bleeding T. 2′ Clotting T. 2.5′	Penicillin Aspirin	T. to 103.5°
5/6/50			A/G = 4.0/3.1 (gm.) BUN 11.2 Creat. 1.1	Penicillin Aspirin	T. to 102.2°
5/7/50				Penicillin Aspirin	T. to 102.2°
5/8/50			BUN 11.2 Creat. 1.2 A/G = 3.7/2.8 (gm.)	Aspirin Pyribenzamine 250 mg.	T. to 101.4°
5/9/50		Platelets 400,000	Blood culture neg. Agglutinations neg. Heterophile antibody neg.	Aspirin Codeine Vitamins	T. to. 104.8° Muscle biopsy normal
5/10/50	Alb. trace Sp.g. 1.014 10–20 granular casts/lpf	Hb. 12.9 gm. RBC 3,830,000 WBC 4,100 (p. 68, l. 26, mono. 4, eos. 2) Platelets 164,000	Ict. ind. 26 BUN 22.4 A/G = 3.6/2.3 (gm.) Prothrombin 22%	Codeine Aureomycin 2.5 gm. Chloromycetin 1.0 gm. Vitamins	T. to 104.8° ECG normal
5/11/50		Hb. 12.1 gm. RBC 3,270,000 WBC 1,720 (p. 58, l. 43) Platelets 116,000	Sed. rate 7 mm./60′	Codeine Aspirin Vitamins	T. to 103°

For explanation of abbreviation see Tables 1, 2, and 4.

regeneration and repair, and the proximate cause of death may have been the cerebral edema. There was no overdosage with cortisone, but it is possible that the use of cortisone precipitated edema of the brain. The donor's febrile reaction was more severe and his clinical condition more serious than in any other donor who has been observed so far.

It is the opinion of consultant pathologists[8,9] that the bone marrow injury in this case was due to an unusual sensitivity reaction, caused by injection of plasma proteins of different specificity. Such reactions have been observed during the war in 1 out of 1,000,000 service men who underwent inoculations in the U. S. Armed Forces.

Discussion. The problems connected with the clinical application of reciprocal blood transfer fall in several categories, which must be considered separately. First, there is the mechanical performance of the reciprocal blood transfer. Second, there is the problem of the organism's reaction to the injection of large amounts of protein. Third, there are the changes observed in the bodily functions as the result of the performance of the procedure. Fourth, there is the selection of proper indications for performance of the procedure and the evaluation of its therapeutic effectiveness. Last, there is the moral and legal problem of subjecting donors to the unknown risks of a reciprocal transfer.

It must be said that the mechanical and hydraulic problems of exchanging large volumes of blood are solved by the cross transfusion procedure. Our method can exchange up to 30,000 cc. of blood per hour; the blood is measured and the exchanges are equalized with an accuracy of 1 cc. in 10,000 cc., the surgical trauma is minimal, the need for heparin not excessive, and the injury to formed elements not appreciable. If a decision is made to perform reciprocal blood transfer, cross transfusion would seem to be the method of choice.

From the immunological point of view, reciprocal blood transfer in man has not yet been investigated. Obviously only carefully cross-matched individuals can be used as partners in this procedure. It is, however, well known that in addition to red cell groups, there are different types of leukocytes and of individual plasmas even within the same general blood group. It is not known how the human organism reacts to injection of large amounts of protein of a slightly different individual specificity. Substitution transfusion and other massive blood transfers use bank blood in which the plasma of many individuals is pooled, and, therefore, they are not comparable procedures. It will be necessary in the future to type and test the plasma of prospective partners of cross transfusion procedures in some manner, perhaps according to the techniques described by Freeman and Schecter[11] and by Levine and State[13]. It is also expected that the use of cortisone and ACTH before, during, and after cross transfusion will enable a sensitive organism to dispose of foreign protein before antibodies are formed, will retard the movement of such protein from the capillaries into the tissues, and will also inhibit the formation of antibodies. It is likely that the complications of cross-transfusion procedures are caused by immunological phenomena which are expected to be susceptible to control. This expectation seems justified in view of the experience of Vecchietti *et al.*, who did 119 cross transfusions without serious reactions of any kind and with a very low incidence of trivial side effects. The reason for the more frequent occurrence of side effects with our method of cross transfusion as com-

pared with the Vecchietti method is not immediately apparent. It may be that the Vecchietti pump, which has no measuring devices and therefore has very short blood conduits, is less destructive to the platelets (cross transfusion equipment is now being constructed here which will shorten our blood conduits by 70% and eliminate a pump altogether). It is also possible that Vecchietti did not encounter undesirable reactions because of the relatively small volumes exchanged (up to 10,000 cc. only). However, it would seem that transfers of 10,000 cc. cause admixture of the blood to the same extent as larger transfers, and when a larger cross transfusion is done the exchange of plasma protein between blood and tissues is not sufficiently rapid to add much transferable protein over and above the amounts contained in the vascular compartments.

There is no evidence that the immunological response to blood administered by the venous route is different from the response to blood administered by the arterial route.

It will be necessary to follow various bodily functions during and after cross transfusion before this method can be accepted more generally. Aside from the side reactions such as fever, it appears that cross transfusion often causes the transitory appearance in the urine of red cells and casts as well as a diminution of renal blood flow, occasional transitory falls in blood pressure, and occasional nausea. The reason for these changes is not immediately evident and awaits investigation. Similar changes have occurred during procedures which involve "handling" of blood, such as dialysis, and therefore they are believed to be due to mechanical factors and not to immunological phenomena.

As for the indications of the procedure and the relative advantages of cross transfusion over related procedures of artificial homeostasis such as exsanguination transfusion, the artificial kidney, and others, it is not possible at this time to make definite statements. It is felt that the procedure would seem indicated in acute nontransmissible diseases of internal organs in which temporary relief might offer a chance for spontaneous recovery. Other indications will certainly become apparent. The unqualified therapeutic success of this procedure in the case of nephrotic syndrome was a surprise. The procedure may yield similar surprises in other clinical entities. Our experience confirms the experience of Italian workers who found vast amelioration of the symptoms and signs of chronic nephritis, toxemia of pregnancy, and hypertension by the cross-transfusion procedure. It is felt at this time that the procedure may be indicated in many otherwise incurable chronic diseases.

We believe that from an ethical point of view it is defensible to offer healthy donors a free choice whether or not they want to subject themselves to the risks inherent in a reciprocal blood transfer. We believe that it is imperative for the donors to be fully acquainted with the history of this procedure, including the cases in which the outcome was unfavorable.

Summary. Reciprocal blood transfer in humans has been performed elsewhere in about 260 persons. Six well documented cases are presented here.

By means of a method of cross transfusion, large volumes of blood (25,000 to 50,000 cc.) have been transferred reciprocally in 6 instances between sick patients and normal donors. The method of cross transfusion was found effective, easy to apply, and safe from a mechanical point of view. Many

excellent therapeutic results of cross transfusion are reported elsewhere and several encouraging cases are reported here. Reactions to reciprocal blood transfer consist of hypotensive phenomena, urticaria, or delayed transitory febrile responses. In one donor, a peculiar syndrome developed about 10 days following a cross transfusion and consisted in severe bone marrow injury; damage to the liver, spleen, and kidney; and death. The causes of these reactions and the possibilities of their avoidance are discussed.

It is felt that cross transfusion may at present be performed only in selected patients for whom no other treatment is available. The donor should be informed about the experimental character and potential risks of the procedure.

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CHANGES IN THE CIRCULATING BLOOD EOSINOPHILS FOLLOWING ACUTE MYOCARDIAL INFARCTION*

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Since Zappert[13], in 1893, reported that eosinopenia was characteristic of certain clinical states, such as febrile diseases, cachexia, and the moribund state, various investigators have noted a decrease in the number of circulating blood eosinophils under a wide variety of conditions. A comprehensive review of the early studies of this problem was published in 1948 by Hills, Forsham, and Finch[7], who presented evidence that the level of blood eosinophils was under the control of the adrenal glands. Following the development by Selye of the concept of the "general adaptation syndrome"[10], and the elucidation of the eosinophil response in the "alarm reaction"[2], many studies were published concerning the blood eosinophil cell and its fluctuations in relation to "stress" and to adrenal and pituitary activity.

Among cardiovascular disease states, eosinopenia has been observed in acute myocardial infarction[6,11], congestive heart failure[4,11], and hypertensive crisis[3]. Concerning the eosinophil counts in acute myocardial infarction, the published data are few. Therefore, a study was undertaken of the fluctuations of the blood eosinophil level in patients with acute myocardial infarction. Information was sought as to: 1) whether an initial eosinopenia was a regularly occurring phenomenon, 2) whether this eosinopenia might be of any diagnostic or prognostic value, and 3) whether secondary falls in the circulating eosinophils might be of use in the early detection of complications occurring during the course of convalescence.

Material and Methods. The patients studied comprised a consecutive series of persons admitted to the hospital with a diagnosis of probable myocardial infarction. Daily early morning determinations of the number of circulating eosinophils in venous blood were performed by a modification of the method of Randolph[8]. Occasional counts, amounting to approximately 5% of those ordered, could not be done for a variety of reasons. The eosinophil counts were reported by noon, daily, and with this information at hand each patient was examined daily. Routine follow-up laboratory procedures, such as total and differential leukocyte counts, erythrocyte sedimentation rates, and repeat electrocardiograms, were performed according to the orders of the attending physician of each patient. However, all patients in whom, following previously normal eosinophil counts, an abnormally low count was reported were subjected to any of the following procedures thought to be indicated: emergency electrocardiogram, portable chest roentgenogram, total and differential leukocyte counts, and daily urinalysis (for blood and urobilinogen) for 4 days. In addition, an emergency eosino-

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phil count was performed on patients clinically suspected of complications.

Following each patient's discharge from the hospital, his chart was reviewed objectively, without reference to the eosinophil counts, to decide whether an unequivocal diagnosis of acute myocardial infarction could be made. At that time the patients were divided into 2 groups. Only those patients who met all of the following criteria were placed in GROUP 1, the myocardial infarction group: 1) serial electrocardiograms showing the progressive changes characteristic of acute myocardial infarction, 2) the temperature curve revealing transient fever, 3) the erythrocyte sedimentation rates being elevated, and 4) the history being such that the time of onset of the acute myocardial infarction could be determined with reasonable accuracy. All other patients were placed in GROUP 2 for analysis. The use of these rigid criteria eliminated from the myocardial infarction group several patients in whom a reasonably certain clinical diagnosis of myocardial infarction could be made. However, it was thought that the data obtained would be more reliable if the final selection of patients eliminated those in whom there was the slightest doubt concerning either the diagnosis or the temporal relation of the acute infarction to the fluctuations of the eosinophil levels.

A total of 51 patients was studied. Of these, 23 patients fulfilled the above criteria for inclusion in GROUP 1. The remaining 28 patients (GROUP 2) had diagnoses as follows (see Table 2): There were 4 patients with a diagnosis of acute myocardial infarction, but in whom the time of onset was vague; 5 with a diagnosis of "probable" myocardial infarction; 11 with protracted angina pectoris (of whom 3 in addition had acute pulmonary edema) but without evidence of myocardial infarction; 3 with chronic congestive heart failure (all mild), 1 of whom, in addition, had an acute gastrointestinal hemorrhage; 1 patient with acute serous pleural effusion of undetermined etiology; and 4 with chest or substernal pain of undetermined etiology and no cardiac disease. Of the 28 patients in GROUP 2 (excluding 2 who died during the 1st week of their illness), 21 had daily eosinophil counts for 6 days or more.

During the analysis of our results, the serious problem arose as to what constituted the normal eosinophil level. Increasing experience has shown that the limits of normal originally proposed by Thorn[12], that is, 100 to 250 eosinophils per c.mm., probably should be broadened. Fisher and Fisher[5] found only 50% of their determinations to be within this range, and, in their series of normal subjects, counts ranged from 5 to 887 per c.mm. They proposed an optimal clinical range of 25 to 300. Best and Samter[1] recommended a normal range of 30 to 250. Thus, the problem of the normal range of the eosinophil count cannot be considered finally settled. An attempt was made, however, to take the average of the opinions quoted, with the realization that exceptions might be frequent. For the purpose of our study, it was decided to consider counts greater than 50 per c. mm. as normal, those from 41 to 50 as probably normal, those from 31 to 40 as probably abnormal, and those 30 or below as definitely abnormal.

Results. Considering the day of the acute myocardial infarction as the 1st post-infarction day, 22 of the 23 patients who fulfilled the criteria enumerated above had daily eosinophil counts begun on or before the 5th post-infarction day. Among these 22 patients, 16 (73%) had a count of less than 30 on one or more of the first 5 days, and 19 (86%) had one count, at least, of less than 40 on one or more of those days (see Table 1). There was a marked variability in the day-to-day levels of the eosinophil counts in the individual patient, as well as among the various patients.

During the period of recovery from the acute myocardial infarction, an occasional patient (Patients 7, 11, and 16, Table 1) had a moderate secondary fall in the eosinophil count (to a level of between 31 and 50 per c.mm.). In no case was this associated with any demonstrable clinical complication. In 3 patients, a secondary fall to less than 30 was encountered. In 1 of these patients (Patient 19, Table 1) a drop in the eosinophil count to 6 on the 16th day following his infarction was associated with the onset of intractable shock leading to his death on that day. Permission for an autopsy was not obtained. In the other 2 patients with the secondary eosinopenia of less than 30 per c.mm. (Patients 2 and 15, Table

TABLE 1.—DAILY EOSINOPHIL COUNTS DURING THE FIRST THREE WEEKS OF HOSPITALIZATION OF PATIENTS WITH DEFINITE MYOCARDIAL INFARCTION

No.	Age and Sex	P.I. Week	Day of Each Week 1	2	3	4	5	6	7	Remarks
1	80 M	1			12		125	203	87	Uncomplicated convalescence
		2	212	175	262	165	75	109	140	
		3	128	115	53	100	93	87	65	
2	56 M	1			0	6	12	100	131	Unexplained eosinopenia on 15th P.I. day
		2	112	112	84	125		138	103	
		3	25	93	100	131	75	118	131	
3	84 M	1		25	53	100	184	125	175	Uncomplicated convalescence. Developed M.I. in June, 1951, and died
		2	150	103	112	143	109	121	131	
		3	168	156	171	100	218	118	150	
4	53 M	1		28	6	21	128	105	146	Persistent pericardial friction rub from 9th to 20th day
		2	131	168	175	209	156	93	234	
		3	125	109	131	68	59	125	112	
5	61 F	1	65	31	43	52	100	118	162	Frequent extrasystoles during second week, controlled by oral quinidine
		2	128	143	143	131	106		70	
		3	106	103	256	134	109	118	131	
6	37 M	1							181	Uncomplicated convalescence
		2	165	218	90	159	256		175	
		3	87	187	175	212	200	159	175	
7	50 M	1		3	3	3	6	25	31	Marked upper abdominal tenderness and muscle guard on 4th and 5th P.I. days. Vertigo, nausea, and vomiting on 14th day
		2	143	78	34	115		187	65	
		3	106	106	167	150	78	68	68	
8	35 M	1					25	21	50	Developed frequent premature beats during 4th week, with no eosinopenia. Died of another M.I. 6 mo. later
		2		50	115	206	168	118	156	
		3	146	184	293	196	225	137	153	
9	61 M	1	0	6	31	46	75	40	100	Uncomplicated convalescence
		2	106	140	118	125	96	137	87	
		3	75	162	150	81	93		159	
10	58 F	1		3	6	37	100	150	137	Uncomplicated convalescence
		2		203	156	94	125	84	106	
		3	121	175	96	193	131	162	96	
11	78 F	1		0	18	43	34	106	37	Congestive heart failure. Gradual decline, died on 20th P.I. day, probably of foreward heart failure. Autopsy. 2 episodes of auricular fibrillation in 2nd P.I. week
		2	59	178	190		137	140	62	
		3	50	39	59	75	60	218		
12*	42 M	1		50	106	212	262	206	256	Uncomplicated convalescence
		2	253	312	353	265	403	365	325	
		3	293	318	300	343	243	240	250	
13	56 M	1		15	0	31	75	262	231	Uncomplicated convalescence
		2	187	234	200	187	143	206	131	
		3	218	256	206	193	187	256	200	
14*	74 M	1	140	106		128	103	115	118	Uncomplicated convalescence
		2	143	168	53	87	175	160	156	
		3	178	106	59	121	137			
15	56 M	1		13	28	50	37	143	162	Frequent extrasystoles during 3rd P.I. week, controlled by oral quinidine
		2	193	212	250	262	281	25	256	
		3	318	210	209	187	168	156	231	
16	58 F	1		18		125	78	68		Severe emotional upset on 18th P.I. day
		2	193	87	100	44	71	29	96	
		3	43	78		68	62	93	56	
17	58 F	1		118	62	9	50	100	62	Uncomplicated convalescence. Eosinophil counts discontinued on 18th day
		2	300	234	325	450	200	512	560	
		3	418	306	318					

TABLE 1.—(*Continued*)

No.	Age and Sex	P.I. Week	Day of Each Week 1	2	3	4	5	6	7	Remarks
18	62 M	1	25	3		25	93	131	100	Uncomplicated convalescence
		2	112	149	146	206	143	193	218	
		3	175	225	262	209	250	193	184	
19	68 M	1				0	0	12	18	Widespread infarct, with congestive heart failure. Digitalized. Persistent fever. Died in intractable shock on 16th P.I. day
		2	31	71	106	87		250	212	
		3	162	6						
20	63 F	1					31	59	156	Uncomplicated convalescence
		2	131	146	165	153	300	200	262	
		3	209	293	168	168	187	246	181	
21	55 M	1				34	87	131	237	Uncomplicated convalescence
		2	281	193	143	153	156	187	87	
		3	125	250	146	137	143	159	184	
22*	54 M	1				227	231	262	331	Uncomplicated convalescence
		2	237	262	218		325	265	159	
		3	212	275	250	193	137	93	387	
23	54 M	1			18	84	171	231	331	Uncomplicated convalescence
		2	306	287	225	268	81	231	293	
		3	234	296	168	284	237	278	328	

P.I. = Post-infarction
M.I. = Myocardial infarction
* Patient who did not have initial eosinopenia

1) no complications could be detected. In both of the latter patients, the eosinophil count was within the normal range on the succeeding day. In GROUP 2, also, such transient moderate or marked eosinopenia without demonstrable cause occurred in occasional patients. That such unexplained eosinopenia should sometimes occur is not surprising. Rud[9], in a very large and well-controlled series, found marked diurnal and short-term (for example, of the order of 5 minutes) variations in the eosinophil count. Fisher and Fisher[5] found levels as low as 5 in a series of 149 normal persons. Consideration must also be given to the significant degree of error which has been shown to be inherent in the method used, even under the most favorable circumstances[1].

Death occurred in 2 of the 23 patients. One of these patients (Patient 19, Table 1) has already been discussed. The other (Patient 11, Table 1) was a 78-year old woman who for 18 mo. had had severe chronic congestive heart failure due to coronary artery heart disease. During her hospitalization she twice developed auricular fibrillation which was successfully terminated by oral quinidine administration. Two minor eosinophil drops were unassociated with these episodes, or with any other clinically detected complications. However, her course was one of gradual decline, and on her last day of life, the 20th post-infarction day, when she had become comatose, her eosinophil count was 218. Death was considered to be due to forward heart failure. Autopsy revealed old and recent myocardial infarcts, and evidence of chronic congestive heart failure.

Among the patients who survived the myocardial infarction, no complications occurred which clinically could be considered serious. In particular, there were no thromboembolic episodes. Minor complications occurred in several patients. Frequent extrasystoles appeared in 3 patients (Patients 5, 8, and 15, Table 1), in 2 of whom they ceased

TABLE 2.—MINIMUM EOSINOPHIL COUNT FOUND DURING THE FIRST WEEK IN PATIENTS WHO DID NOT FULFILL THE CRITERIA FOR INCLUSION IN GROUP 1, AND THEREFORE WERE PLACED IN GROUP 2 (SEE TEXT)

No.	*Age, Sex*	*Diagnosis*	*No. of Days on which Daily Eosinophil Counts were Done*	*Lowest Eosinophil Count in 1st Week*	*Remarks*
24*	79 F	M.I., indefinite time of onset, severe pulmonary edema, bronchopneumonia	3	0	Did not respond to treatment. Died on 3rd hospital day. Autopsy
25	37 M	M.I., indefinite time of onset	26	198	
26	55 M	M.I., indefinite time of onset	14	156	
27	59 M	M.I., indefinite time of onset	33	212	Patient died in a subsequent attack 3 months later. Autopsy revealed* old and recent myocardial infarcts
28*	72 F	Recent M.I., probable	2	0	Died on 2nd hospital day. No autopsy
29	63 M	Recent M.I., probable	18	13	
30	56 F	Recent M.I., probable	5	43	
31	56 M	Recent M.I., probable	29	3	
32	45 M	Recent M.I., probable	33	6	
33	57 M	Protracted angina pectoris	6	87	History of old M.I.
34	50 M	Protracted angina pectoris	10	71	History of old M.I.
35	54 M	Protracted angina pectoris	4	190	
36	46 M	Protracted angina pectoris	20	31	History of old M.I.
37	74 M	Protracted angina pectoris	19	193	
38	75 M	Protracted angina pectoris	28	71	History of angina pectoris on exertion for many years. Rapid auricular fibrillation at onset of pain
39	37 F	Protracted angina pectoris	4	146	
40	52 M	Protracted angina pectoris	36	81	History of old M.I.
41	74 M	Protracted angina pectoris, acute pul. edema	3	3	
42	68 F	Protracted angina pectoris, acute pul. edema	20	0	
43	57 M	Protracted angina pectoris, acute pul. edema	11	6	History of old M.I.
44	59 M	Acute serous pleural effusion, etiology unknown	6	42	
45	64 F	Recent G.I. hemorrhage, anemia, mild congestive heart failure	9	62	History of old M.I.

TABLE 2.—(*Continued*)

No.	*Age, Sex*	*Diagnosis*	*No. of Days on which Daily Eosinophil Counts were Done*	*Lowest Eosinophil Count in 1st Week*	*Remarks*
46	60 M	Rheumatic heart disease, chronic auricular fibrillation, mild congestive heart failure	2	275	
47	68 F	Arteriosclerotic heart disease, mild congestive heart failure	31	112	
48	60 M	Undiagnosed chest pain, no cardiac diagnosis	13	243	
49	58 F	Undiagnosed chest pain, no cardiac diagnosis	10	40	
50	74 F	Undiagnosed chest pain, no cardiac diagnosis	18	6	"Pathological gall bladder" (radiological diagnosis)
51	49 F	Undiagnosed chest pain, no cardiac diagnosis	13	60	

M.I. = Myocardial infarction
Pul. = Pulmonary
G.I. = Gastrointestinal
* Patient died during his hospitalization

following quinidine therapy. In 1 patient (Patient 4, Table 1), the only one in whom pericarditis was detected, a pericardial friction rub appeared on the 9th day, and persisted until the 20th day. One patient (Patient 7, Table 1) had an episode of vertigo, nausea, and vomiting lasting 1 day, and 1 patient (Patient 16, Table 1) had a severe emotional reaction when informed of the death of her mother. In none of these patients was the episode in question accompanied by eosinopenia.

The 28 patients in GROUP 2 showed a variable eosinophil response (see Table 2). The 5 cases of "probable" recent myocardial infarction (Patients 28 through 32, Table 2), of whom 4 had a pronounced early eosinopenia, were omitted from GROUP 1 only because the electrocardiographic alterations were atypical. Clinically, all 5 were diagnosed and treated as acute myocardial infarction. There was 1 patient (Patient 24, Table 2) who entered the hospital with a diagnosis of acute pulmonary edema and bronchopneumonia in addition to a possible myocardial infarction, who failed to respond to treatment, and died on her 3rd hospital day. An eosinophil count of 0 persisted during her hospital stay. She was shown at autopsy to have recent and old myocardial infarcts, bronchopneumonia, and congestive heart failure. Among the 11 patients finally diagnosed as having protracted angina pectoris without myocardial infarction (Patients 33 through 43, Table 2), only 4 had early eosinopenia. Three of these 4 had entered the hospital with acute pulmonary edema. The 4th patient, whose minimum count was 31 in the 1st week, continued to have a relatively low eosinophil count which never went above 64 during his entire hospital stay of 3 weeks. The only other patient in GROUP 2 with an initial eosinopenia (Patient 50, Table 2) was one with a known duodenal ulcer and a "pathological gallbladder" (roentgenographic diagnosis), who entered the

hospital with slight fever and with a severe sharp anterior mid-chest pain radiating to the mid-back. The pain, although not definitely diagnosed, was thought to be due to biliary colic.

Discussion. Our findings in patients with acute myocardial infarction indicate that, although there is usually an early eosinopenia, it is not invariably present, and therefore, as a diagnostic criterion in early myocardial infarction, the eosinophil count has only a very limited application. Although it is true that eosinophil counts in the definitely or probably abnormal range occurred during the first post-infarction week in most of our patients, 3 (14%) of our 22 patients with unequivocal diagnoses of acute myocardial infarction failed to have early eosinopenia (Patient 6, Table 1, whose counts were not begun until the 6th post-infarction day, is not considered here). While studies of pituitary and adrenal metabolism were not performed, and allergy studies were not carried out, there was no cause for a clinical suspicion of either endocrine or allergic disorders as an explanation for the lack of eosinopenia. The fact that all 3 of these patients had uncomplicated recoveries might mean that the lack of eosinopenia was on the basis of mildness of the illness. However, several patients with pronounced early eosinopenia had recoveries which were equally uncomplicated. In 1 of the 3 patients (Patient 21, Table 1) counts were not begun until the 4th post-infarction day. As in several other patients, an early eosinopenia might have been terminated by that time. The other 2 patients (Patients 12 and 14, Table 1) had their counts begun on the 2nd and 1st post-infarction days, respectively. Our findings thus indicate that even in the absence of clinically apparent endocrine or allergic disorders, the absence of initial eosinopenia does not rule out the possibility of acute myocardial infarction. Moreover, because eosinopenia occurs in such a wide variety of acute conditions, it is obvious that the presence of eosinopenia following an episode suspected of being an acute myocardial infarction adds little weight to the diagnosis. Our results in patients without acute myocardial infarction bear out this impression. Acute pulmonary edema, in particular, was seen in our patients to be especially prone to result in extreme eosinopenia.

In regard to prognosis, no consistent correlation was found between the early eosinophil fluctuations and the clinical course. It has already been pointed out that, although those patients without initial eosinopenia had uncomplicated recoveries, other patients who did have early eosinopenia had equally uncomplicated recoveries. Conversely, although both of the patients who eventually died of their infarcts had pronounced early eosinopenia, other patients with uneventful recoveries also had pronounced early eosinopenia. Thus, no prognostic implications are warranted on the basis of the early eosinophil response in patients with acute myocardial infarction.

Because of the paucity of serious secondary complications in our series, no statement is possible concerning the behavior of the blood eosinophil level in the presence of serious complications of acute myocardial infarction. The small amount of information concerning this subject was discussed previously. Secondary moderate or marked transient drops in the eosinophil count were seen occasionally without any clinically apparent cause; this also has been discussed.

Summary and Conclusions. 1. Daily blood eosinophil counts were performed for varying periods of time in a series of 51 patients, 23 of whom had

acute myocardial infarction, the onset of which could be accurately timed, the remaining 28 of whom had other diagnoses. All had had an admission diagnosis of suspected acute myocardial infarction.

2. Although the majority of the patients with acute myocardial infarction had an initial eosinopenia of variable degree, the eosinopenia was not encountered consistently enough to be of differential diagnostic significance. Patients were seen occasionally without eosinopenia in the presence of acute myocardial infarction, and frequently with eosinopenia in the absence of acute myocardial infarction.

3. In the patients with acute myocardial infarction there was no consistent correlation between the degree and duration of the initial eosinopenia and either the clinical severity of the illness or the ultimate prognosis.

4. Too few major complications were seen to warrant any statement concerning the behavior of the eosinophil count in the presence of such complications. In the presence of complications classified as "minor," eosinopenia was not seen. Moderate or pronounced transient eosinopenia was occasionally encountered in the absence of any apparent clinical cause.

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EFFECT OF DISEASE ON ERYTHROCYTE AND PLASMA POTASSIUM CONCENTRATIONS*

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The fasting plasma potassium concentration of normal man is maintained within rather narrow limits[6]. It is, however, subject to a number of physiological influences and may be either increased or decreased in various disease states. Since the plasma potassium level may be altered acutely and since the concentration of potassium in the cells is much greater than in the plasma, the plasma potassium level does not necessarily reflect the state of the body stores of this ion.

The most accurate method of estimating the total potassium content of the body involves the measurement of the volume of distribution of isotopic potassium[1], a procedure that is not practical as yet for general clinical use. Since erythrocytes are readily available and since the red blood cell potassium content probably reflects to some degree the general intracellular potassium stores, a comparison has been made between the plasma and erythrocyte potassium levels in a number of disease states. Simple techniques, available to any laboratory equipped with a flame photometer, were used.

Low red blood cell potassium levels have been reported in diabetic acidosis[3,7,10], loss of gastrointestinal contents[12,13], postoperative states[5], and renal disease[8,11]. Low erythrocyte potassium level has also been reported in familial periodic paralysis[2], a condition in which no external potassium loss occurs. The low erythrocyte potassium in this condition probably represents a redistribution to other tissues.

Methods. Venous blood, obtained from subjects before breakfast, was used for all analyses. Whole blood to which no anticoagulant had been added was hemolyzed by placing 1 cc. in a flask containing 96 cc. of distilled water. Three cubic centimeters of lithium standard were subsequently added for analysis on the flame photometer. Heparinized blood can be used for this step, if sodium is not to be measured. Plasma, separated within 15 minutes from the erythrocytes of a heparinized blood sample, and serum were analyzed for potassium and sodium, respectively. All measurements were made on an internal standard flame photometer. Mutual interference between sodium and potassium occurs in flame photometry when these ions are present in high concentration. Corrections were made from observations on the interfering effects of known amounts of sodium and potassium. The corrections were generally less than 1 mEq./L. and can be ignored for ordinary purposes.

Hematocrits were measured in duplicate in Wintrobe tubes using heparinized blood. Four milligrams of dried heparin per 10 cc. of blood were used instead of the recommended 2 mg. per 10 cc. of blood[9]. The error introduced by this modification was compensated by centrifugation at 739 x G for 1 hour instead of the usual 905 x G for 1 hour.

Blood cell potassium was calculated from the relation: Whole Blood Potassium-Plasma Potassium x (1-Hematocrit) + Blood Cell Potassium x Hematocrit.

Water content of whole blood and serum was determined by desiccation to constant weight in an oven at 100° C. This generally took 72 hours. Erythrocyte water was then

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calculated from the relation: Whole Blood Water = Plasma Water × (1-Hematocrit) + Erythrocyte Water.

REPRODUCIBILITY. Minimal error in hematocrit is essential for this method of measuring erythrocyte potassium content. The mean percentile difference in hematocrit between duplicates of 100 samples of blood was 0.79.

Variations produced by errors inherent in the method were evaluated by comparing blood samples obtained 30 minutes apart. The mean percentile differences in 11 such studies were as follows: hematocrit 1.05, erythrocyte potassium concentration 0.95, plasma potassium 2.27, serum sodium 0.51, erythrocyte water 0.76, serum water 0.11, erythrocyte water potassium level 0.69, plasma water potassium 2.08, and serum water sodium 0.46.

Results. The concentration of potassium in cells and plasma and in cellular and plasma water, observed in 14 patients who had no evidence of disease that might produce electrolyte abnormalities, are shown in Table 1. None of these subjects had gastrointestinal, metabolic, hepatic, renal, or infectious diseases. Also shown are the hematocrits, erythrocyte and serum water contents, and the concentrations of sodium in serum. Except for the hematocrits, all values fall within the normal ranges reported by other laboratories. Relatively little variation occurred among these subjects in any category. Several patients with moderate to severe anemia were included, but their data were indistinguishable from the rest of the group.

TABLE 1.—THE POTASSIUM CONTENT OF CELLS AND PLASMA OF 14 FASTING NORMAL SUBJECTS

Patient Number	*Hematocrit (% Cells)*	*Potassium (mEq./L.)*		*Serum Sodium (mEq./L.)*	*Water (% Wt)*		*Potassium (mEq./L. Water)*	
		Cell	*Plasma*		*Cell*	*Serum*	*Cell*	*Plasma*
1	47.3	91.4	4.3	140	64.6	90.6	142	4.7
2	46.7	91.0	4.3	141	63.4	91.5	144	4.7
3	46.2	96.3	4.3	139	65.6	91.2	147	4.7
4	46.1	92.7	4.4	140	65.6	91.2	141	4.8
5	45.0	89.9	4.9	136	64.9	91.5	138	5.4
6	44.1	95.2	4.2	140	66.3	91.7	144	4.6
7	41.3	100	5.4	139	66.3	91.7	152	5.9
8	41.2	97.5	4.3	139	65.8	91.0	148	4.7
9	39.4	100	4.5	136	66.8	92.2	150	4.9
10	37.2	99.3	4.5	142	66.4	91.5	150	4.9
11	35.7	95.0	3.7	132	65.8	92.3	144	4.0
12	27.7	91.0	4.6	136	63.4	93.0	144	5.0
13	27.2	92.2	3.8	137	63.9	91.2	144	4.2
14	16.4	90.9	4.2	135	64.0	92.1	142	4.6
Mean		94.5	4.4	138	65.2	91.6	145	4.8
σ		3.6	0.4	2.6	1.2	0.6	3.5	0.4

Twenty-one observations among 19 patients who had abnormal potassium levels in either the plasma or erythrocytes are recorded in Table 2. Also included in this table are the data from 8 patients who had normal potassium values, although they had various diseases that conceivably might have produced abnormal potassium metabolism. To be classified as abnormal, a value outside the mean normal plus or minus 2 σ was required. All possible combinations of high, normal, and low plasma and erythrocyte potassium levels occurred, except no instance in which

TABLE 2.—THE POTASSIUM CONTENT OF CELLS AND PLASMA OF PATIENTS WITH DISTURBED POTASSIUM METABOLISM

Patient Number	Diagnosis	Potassium (mEq./L.) Cell	Potassium (mEq./L.) Plasma	Serum Sodium (mEq./L.)	Water (% Wt) Cell	Water (% Wt) Serum	Potassium (mEq./L. Water) Cell	Potassium (mEq./L. Water) Plasma
Mean 14 Normals		94.5	4.4	138	65.2	91.6	145	4.8
Mean $+2\ \sigma$		101.7	5.2	143	67.6	92.8	152	5.6
Mean $-2\ \sigma$		87.3	3.6	133	62.8	90.4	138	4.0
	Potassium Low in Cells, High in Plasma							
15	Renal failure	82.3	9.0	138	62.9	91.1	131	9.9
16	Renal failure	85.6	7.3	133	63.6	91.4	135	8.0
17	Renal failure	82.3	7.0	109	67.0	92.2	123	7.6
18	Renal failure	85.3	6.1	110	67.6	93.3	126	6.5
	Potassium Low in Cells, Normal in Plasma							
19	Addison's, no therapy	82.0	5.0	116	67.4	91.4	122	5.5
20	Renal failure	83.7	4.9	116	68.0	91.7	123	5.3
21	Diabetes, insulin resistant	87.3	4.7	137	66.2	90.6	132	5.2
17	Renal failure	85.8	4.0	127	66.0	92.1	130	4.4
	Potassium Low in Cells, Low in Plasma							
22	Diarrhea	81.8	3.3	138	68.3	92.8	120	3.6
23	Renal failure	80.7	3.2	124	66.3	92.1	122	3.5
24	Nephritis	84.6	3.2	135	65.5	90.5	129	3.5
25	Renal disease	87.8	3.1	117	67.7	91.5	130	3.4
	Potassium Normal in Cells, High in Plasma							
26	Renal failure	91.5	6.4	114	69.6	91.2	132	7.8
27	Cirrhosis	93.6	5.6	129	67.3	91.1	152	6.2
28	Cirrhosis	93.2	5.6	129	65.7	93.2	143	6.0
	Potassium Normal in Cells, Low in Plasma							
29	Vomiting	95.0	3.1	127	67.1	92.5	142	3.4
30	Diarrhea	100	3.1	145	64.3	92.2	159	3.4
31	Diarrhea	101	2.8	131	69.9	90.8	144	3.1
27	Vomiting	96.0	2.4	137	66.4	92.3	145	2.6
	Potassium High in Cells, Normal in Plasma							
32	Renal failure	103	5.0	137	68.7	92.2	150	5.4
	Potassium Normal in Cells and Plasma							
34	Vomiting Renal disease	95.5	5.2	129	64.8	91.7	147	5.7
35	Myocardial Infarct	90.0	4.9	139	66.0	91.0	136	5.4
36	Bronchiectasis	93.7	4.8	138	66.3	91.3	141	5.3
37	Hepatic failure	99.2	4.8	124	59.5	92.3	167	5.2
38	Renal failure	95.0	4.6	141	65.6	93.2	145	4.9
39	Leukemia	97.5	4.5	136	70.4	92.3	139	4.9
40	Hypogonadism	96.4	4.4	126	67.0	92.8	145	4.7
41	Heart failure	90.2	4.1	138	64.9	90.9	139	4.5

potassium was elevated in both phases was observed. Low potassium concentration in the cells was much more common than high cellular levels. Increased plasma potassium with low or normal levels in the cells was not uncommon, especially in patients with renal failure who had frequent vomiting and poor dietary intake.

In only a few instances was there a significant difference, as compared to the respective normal values, between the erythrocyte potassium concentration calculated per liter of cells and per liter of cell water. Thus, the potassium content per liter of cells in Patient 25 was not quite outside the mean normal minus 2 σ, but the con-

TABLE 3.—EFFECT OF CHANGES IN DISEASE PROCESSES OR THERAPY ON THE POTASSIUM CONTENT OF CELLS AND PLASMA

Patient Number	*Diagnosis*	*Therapy*	*Date*	*Potassium (mEq./L.) Cells*	*Plasma*	*Serum Sodium (mEq./L.)*
42	Lymphosarcoma	None	11/17	91.0	4.6	136
		ACTH	11/27	92.8	4.6	138
		ACTH	12/6	94.3	4.7	137
		ACTH	12/14	94.5	4.5	140
		ACTH	12/20	94.4	4.8	140
		ACTH	12/28	96.7	4.9	140
		None	1/10	95.8	4.7	141
43	Purpura	None	12/12	99.3	4.5	142
		ACTH	12/20	99.7	4.3	140
		ACTH	12/28	103.0	4.6	142
		ACTH	1/10	99.8	4.1	139
19	Addison's Disease	None	12/12	82.0	5.0	116
		NaCl+DCA	12/15	92.3	3.7	130
		NaCl+DCA	1/4	95.2	2.7	138
		NaCl	1/17	97.6	4.4	132
24	Nephritis	K supplement	10/19	84.6	3.2	135
		Low K diet	10/23	84.9	2.9	136
		Low K diet	10/28	79.6	1.9	134
		Low K diet	11/1	74.4	1.6	133
		K supplement	11/4	84.4	2.4	134
		K supplement	11/8	86.0	3.2	136
15	Renal Failure	None	8/15	82.3	9.0	138
		None	8/16	84.4	8.2	141
		None	8/17	77.6	7.3	140
		None	8/22	77.0	6.6	132
16	Renal Failure	None	11/27	85.6	7.3	133
		None	12/1	85.9	7.2	134
		None	12/5	81.1	10.0	121
18	Renal Failure	None	11/4	85.3	6.1	110
		None	11/6	80.6	6.3	111
		None	11/8	83.6	6.4	112
23	Renal Failure	None	10/14	80.7	3.2	124
		K supplement	10/15	83.8	3.2	126
		K supplement	10/17	92.5	3.3	140
		K supplement	10/19	97.2	3.6	142
		K supplement	10/21	101.0	4.4	143
17	Renal Failure	Vomiting	8/17	82.3	7.0	109
		Improving	8/19	79.0	5.4	120
		Improving	8/22	85.8	4.0	127
		Recovered	9/14	93.9	5.0	135

centration per liter of cell water was well below the normal range. A somewhat similar situation was observed in Patient 26, but the level per liter of cells was so near the mean normal value that this patient's data were classified in the normal cellular potassium group. Conversely, Patients 30 and 37 had normal potassium levels per liter of cells, but above-normal values when calculated per liter of cell water.

Serum sodium was abnormally low in a number of the patients recorded in Table 2, but bore no relation to the potassium level in either cells or plasma. Three of the patients with normal potassium levels in cells and plasma had abnormally low serum sodium levels.

Serial observations were obtained in several patients and are recorded in Table 3. Patients 42 and 43 with normal electrolytes were given full therapeutic courses of ACTH. No significant change in any electrolyte concentration occurred in either patient. Patient 19 with untreated Addison's disease had decreased sodium in the serum and potassium in the cells. Therapy with salt and DOCA returned these values to normal while the plasma potassium decreased sharply from a high normal value.

Patient 24[4], with potassium-losing nephritis, was placed on a low potassium diet. Potassium in both cells and plasma decreased, but returned to the former values when large supplements of potassium were added to the diet. The potassium balance was measured during these observations. Calculations based on the concentration of potassium in plasma water and in the erythrocytes, and on the assumptions that extracellular and intracellular fluid were 17.5 and 40% of body weight, respectively, indicated that the potassium deficit was only 60% of that actually observed at the end of the low-potassium intake period. Thus, the erythrocytes do not lose as much potassium as do certain other cells.

The cellular potassium concentrations in Patients 15, 16, and 18 with terminal renal failure changed but little during repeated observations, although the plasma potassium increased in one and decreased in another. The abnormally low cellular potassium concentrations in Patient 23 with terminal renal failure returned to normal during a period of potassium supplementation, although no clinical improvement occurred. The initial plasma potassium in this patient was abnormally low and also rose to normal during potassium administration but at a slower rate than did the cellular level. Low cellular potassium levels in Patient 17 returned to normal as he recovered from acute renal failure which had been associated with vomiting and poor dietary intake. Again, close correlation between the changes in cell and plasma did not obtain.

Discussion. Although the content of potassium varies in different tissues, the concentration in the erythrocytes probably reflects the total body store of potassium under most circumstances. That this is the case is suggested by the observations on Patients 24, 23, and 17. That the concentration of potassium in the plasma can vary independently of its concentration in the erythrocytes is demonstrated by the data presented above. The plasma potassium level, therefore, does not necessarily reflect the state of the body stores of potassium. This has important implications for the treatment of patients with disturbed potassium metabolism.

The estimation of the erythrocyte potassium level is quite simple and requires only the measurement of potassium in plasma and whole blood and the hematocrit. The erythrocyte potas-

sium level in normal fasting subjects is quite constant. The mean level in 14 subjects was 94.5 mEq./L. of cells, $\sigma = 3.6$ mEq./L. of cells. Calculation of potassium per liter of cell water is not necessary for routine clinical purposes.

Summary. 1. A simple reproducible technique for the measurement of the erythrocyte potassium level is described.

2. The mean erythrocyte potassium level in 14 fasting normal subjects was 94.5 mEq./L. of cells, $\sigma = 3.6$ mEq./L. of cells.

3. Twenty-one observations in 19 patients with disturbed potassium metabolism indicate that the plasma potassium level does not necessarily reflect the erythrocyte potassium concentration.

4. The erythrocyte potassium level appears to reflect the direction of changes in the body stores of potassium.

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ARGENTAFFIN CELLS AND PERNICIOUS ANEMIA

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In the course of time, widely divergent theories have been advanced concerning the function of the argentaffin cells in the digestive tract. Among these, in recent years, one in particular (the theory about the significance of these cells to hematopoiesis) has been gaining ground in the medical literature. This theory may be credited to Erös and Jacobson. Erös[8] stated that he found atrophy of the argentaffin system in the intestinal tract in patients who had died of pernicious anemia, and on this basis he advanced the hypothesis that the argentaffin cells in the gastrointestinal tract and similar cells in other organs play a certain role in hematopoiesis. In a number of papers, Jacobson[15a,b] and Jacobson and his co-workers[16,17] likewise presented the view that the argentaffin cells in the gastrointestinal tract play a part in the normal erythropoiesis.

This view is based on what Jacobson[15a] calls "the striking parallelism in the distribution of the argentaffin cells of man and the pig and the localization of the principle active against pernicious anemia in the mucosa of the gastrointestinal tract". He further found no, or practically no, argentaffin cells in cases of pernicious anemia and sprue with macrocytic anemia. As a result of his chemical studies Jacobson believed that the yellowish cytoplasmic granules of the argentaffin cells contain a pterin compound. These compounds show an intense fluorescence with ultraviolet rays and a fluorescence spectrum of the pterin type was also found to be emitted from purified liver extracts[16b]. Further evidence that pterin compounds are associated with the formation of erythrocytes is adduced by the observation of the relation of these substances to folic acid[26,30].

For his histological studies[15a] Jacobson employed Hamperl's[13a] modification of the Masson technique (reduction of ammoniacal silver nitrate) and the "kernechtrotsalz B" method (Clara[5]), a diazo staining method. With regard to the distribution of the argentaffin cells in man, it is briefly stated that they are practically absent in the fundus, always found in fair numbers in the pyloric region, and most numerous in the duodenum. They are also found in Brunner's glands. A similar distribution is found in the hog.

As to the localization of the hemopoietic active principle in man and the hog the reader is referred to works by Meulengracht[25a], Uotila[34] and Schemensky[27]. Since these works, however, the literature on the localization of the hemopoietic active principle has been supplemented by essential points, and the previous views have been modified in part (cf. Table 1). It may be added that recent observations[1,2,12] seem to indicate that the extrinsic food factor of Castle and Vitamin B_{12} are either identical or closely related substances, and that Vitamin B_{12} (or a closely related substance) and intrinsic factor together constitute the effective hemopoietic agents in hog gastric and duodenal tissue[2]. Furthermore, other investigators[10,13b,18a,b] have not arrived at the same results as Jacobson with regard to

the distribution of the argentaffin cells in the human stomach.

In view of these conflicting observations, it appeared reasonable to re-investigate the question about a possible "striking parallelism" in the distribution of the argentaffin cells and the localization of the principle active against pernicious anemia in the mucosa of the digestive tract, in particular the fundic and pyloric portions of the stomach and the duodenum, in man and the hog.

TABLE 1.—THE LOCALIZATION OF THE HEMOPOIETIC ACTIVITY IN FUNDUS, PYLORUS, AND DUODENUM OF MAN AND THE HOG ACCORDING TO VARIOUS AUTHORS

Region or Substance	*Anti-pernicious Anemia Effect*	*No Anti-pernicious Anemia Effect*
	Man	
Fundus	Fox and Castle[9] Landboe-Christensen and Plum[21a,b]	
Pylorus	Fox and Castle[9] Landboe-Christensen and Plum[21b]	
Duodenum	Landboe-Christensen, Berk and Castle[19]	
Duodenal secretion		Castle, Townsend and Heath[3]
Jejunum		Landboe-Christensen, Berk and Castle[19]
	Hog	
Fundus		Meulengracht[25a,b,d] Ungley[33] Fox and Castle[9]
Pylorus	Meulengracht[25a,b,d] Ungley[33] Fox and Castle[9]	
Pure pyloric secretion	Landboe-Christensen and Wandall[22]	
Duodenum	Meulengracht[25a,c,d] Sharp, McKean, and Heide[28]	
Pure duodenal secretion	Landboe-Christensen and Bohn[20]	

Previous Studies on the Occurrence of Argentaffin Cells. In the course of time many investigators have dealt with the occurrence of argentaffin cells (basal granular cells, entero-chromaffin cells, yellow cells) in the intestinal epithelium, but few have studied these cells in the human stomach.

Hamperl[13b], employing the Masson-Hamperl silver technique, states that in normal or apparently normal stomachs there are few, if any, argentaffin cells. Cases in which argentaffin cells were abundant were always associated with pronounced symptoms of chronic gastritis. The increased number of argentaffin cells was found in islands of intestinal mucosa in the stomach and also in glands of the fundic and mostly the pyloric types. According to Hamperl, abundance of argentaffin cells in the human gastric mucosa indicates epithelial "misregeneration".

Gillman[10], who employed the same silver technique in his studies on material originating from Bantu Negroes, reports that no cells which could be regarded as argentaffin ("basal granular cells") were identified in the stomach, whereas they were particularly abundant in the first part of the duodenum. Gillman quotes the theory of Jacobson about the parallelism be-

tween the distribution of argentaffin cells and the localization of the principle active against pernicious anemia, and he states that a frank case of pernicious anemia has as yet never been described in a Bantu. On these grounds alone, he says, there would have been every reason to expect that the basal granular cells should have been very numerous in the stomachs of normal Bantu. But they are absent or so few in number that they have escaped identification.

For the demonstration of silver staining cells in the stomach other methods have been used by Dawson[7a,b,c], Sharples[29] and Ceranke and Feyrter[4]. Through these methods, however, besides the argentaffin cells other cells also are impregnated (argentophile cells: cf. Dawson[7c]).

In his study of the histochemistry of the argentaffin cells, Gomori[11] describes and depicts cells, stained after a methenamine silver method, in the human fundus and antrum. These cells are stated to differ from the well known, typical entero-chromaffin cells by being small, polyhedral, or elongated, or showing bizarre star or spider shapes. According to Gomori the presence of pteridine in the entero-chromaffin cells cannot be demonstrated with histochemical methods now available.

Concerning argentaffin cells in the hog, besides the brief statement by Jacobson[15a], only a few reports are found in the literature. Tang[31] states that the number of "yellow" argentaffin cells is particularly high in the duodenum of the hog, and Tehver[32] reports on the shape and the number of these cells in the fundus, pylorus, and duodenum.

Material and Methods Used by Writer. The human material employed in this study consisted of parts of the stomach and duodenum removed surgically and fixed in 10% formaldehyde solution immediately after their removal. The portions examined (fundus, pylorus, and duodenum) originating from 50 individuals, presented in some cases a perfectly normal mucosa, while various degrees of inflammatory changes were seen in other cases.

The hog material was obtained from slaughtered animals of American and Danish races. The fixation in 10% formaldehyde solution took place as quickly as possible after the animal was killed, usually within ½ hour. In some cases the specimens were removed operatively and fixed immediately after the removal. The fundus, pylorus, and duodenum from 12 hogs were examined.

With regard to comparison with previous works, especially the findings reported by Jacobson, the following account will give merely the results obtained by employment of the Masson–Hamperl technique, reduction of ammoniacal silver nitrate, for the demonstration of argentaffin cells in the stricter sense of the term. According to Lison[23] this term applies only to cells in which the reducing substance is present within the cell and is capable by itself of producing a reduction of ammoniacal silver hydroxide without addition of any reducing agent. Thus the argentaffin reaction is esentially different from the various forms of silver impregnation in which it is necessary besides the silver compound to add a reducing agent in order to obtain a precipitation of silver (cf. Dawson[7c] and Lison[23]).

Results. It would be going too far here to enter into all the cytological details and hence only certain conspicuous features will be mentioned.

FINDINGS IN MAN. In man the argentaffin cells attain their highest degree of development in the duodenal mucosa. Here they are most numerous and also largest and are of the general intestinal type (Fig. 1). In Brunner's glands, on the whole, there are few argentaffin cells. In the human stomach the argentaffin cells have developed but slightly. Most sections from the pylorus show a varying number of more or less inconspicuous, peripherally located, thin, linear, or crescent-shaped argentaffin elements. In tangential sections they often appear as membranous and irregularly

branching, with thin (sometimes anastomosing) processes (Fig. 2). They are finely granulated. Morphologically they show no resemblance to the intestinal argentaffin cells, but with their localization (periglandular, subepithelial) and form they often remind one somewhat of basket cells. In the pyloric part of the stomach, occasionally also in gastric mucosa containing both pyloric and fundic glands, ectopic "islands" of intestinal epithelium and glands are found not infrequently. Besides the characteristic ordinary intestinal epithelium, these islands contain goblet cells, sometimes Paneth cells, and almost constantly argentaffin cells of intestinal type. As a rule these latter cells are conspicuous, plump, and larger than the usual intestinal argentaffin cells and often quite numerous, making the islands stand out very conspicuously on the background of the surrounding pyloric mucosa (Fig. 3). Also in the fundus of the human stomach the argentaffin cell is poorly developed. No argentaffin cells of intestinal type are seen here. On the whole, the Masson-stainable elements are rather few and scattered; but in most sections some elongated linear, often curved or irregularly branching, elements are seen that here and there may remind one of the above-mentioned findings in the pylorus.

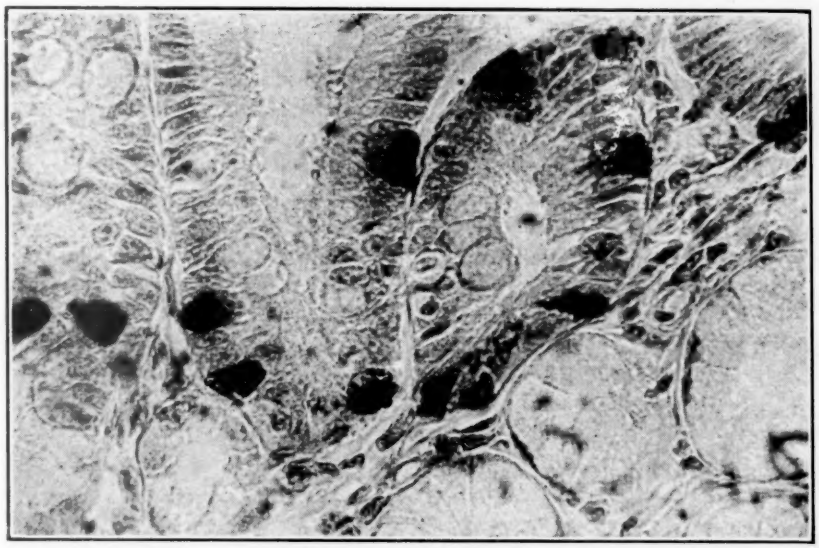

FIG. 1.—Longitudinal and cross section through duodenal crypts of man, showing abundance of argentaffin cells, rather big, of the ordinary intestinal type. The clear zone under the crypts contains Brunner's glands. Fixation with formaldehyde solution. Silver technique by Masson–Hamperl. No counterstain. X700. (The other specimens were treated in the same way.)

FINDINGS IN HOG. In the hog, just as in man, the argentaffin cells in the duodenum are of the intestinal type, larger and well developed. The granulation forms a triangle with its base on the basal membrane and it is found not only in the basal part of the cell, as in man, but extends all around and beyond the nucleus, enveloping the latter. In the pylorus (Fig. 4) the argentaffin cells are likewise well developed, of the intestinal type, and

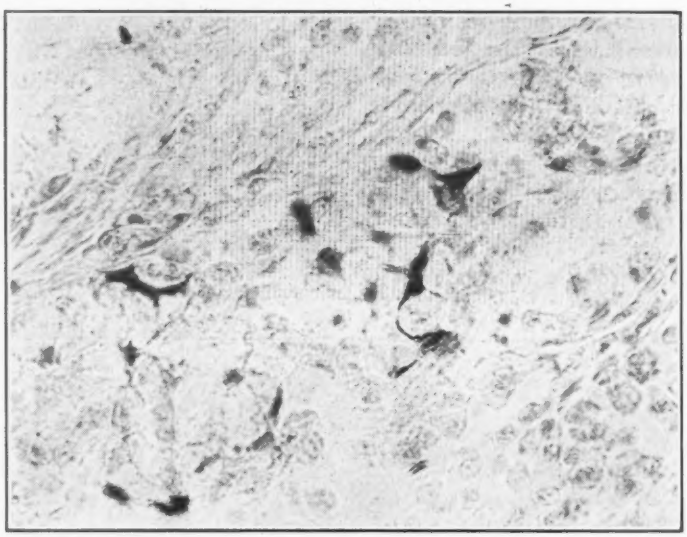

FIG. 2.—Pyloric glands of man tangentially cut, showing irregular, sheetlike, star-shaped, branching, and anastomosing argentaffin cells.

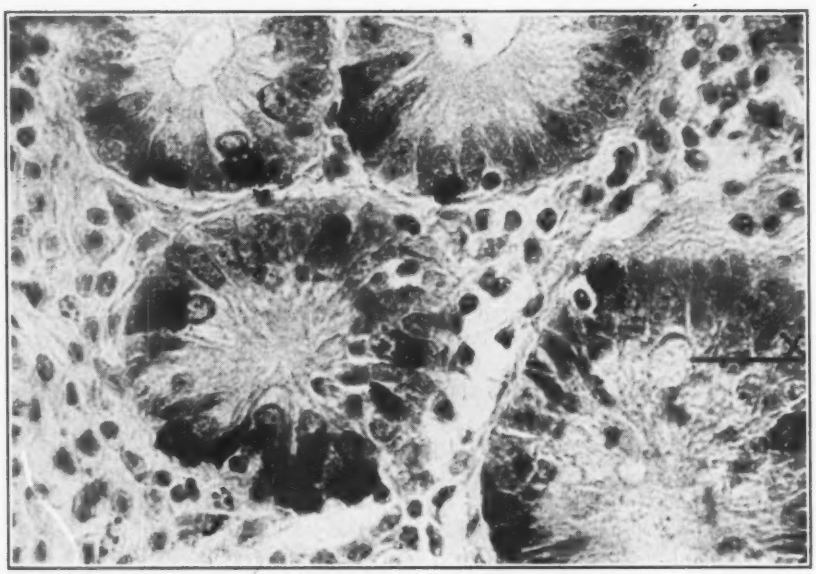

FIG. 3.—Pyloric mucosa of man. Ectopic intestinal island with cross cut crypts. Abundant big, plump argentaffin cells of intestinal type among typical intestinal epithelial cells. Among these, goblet cells.

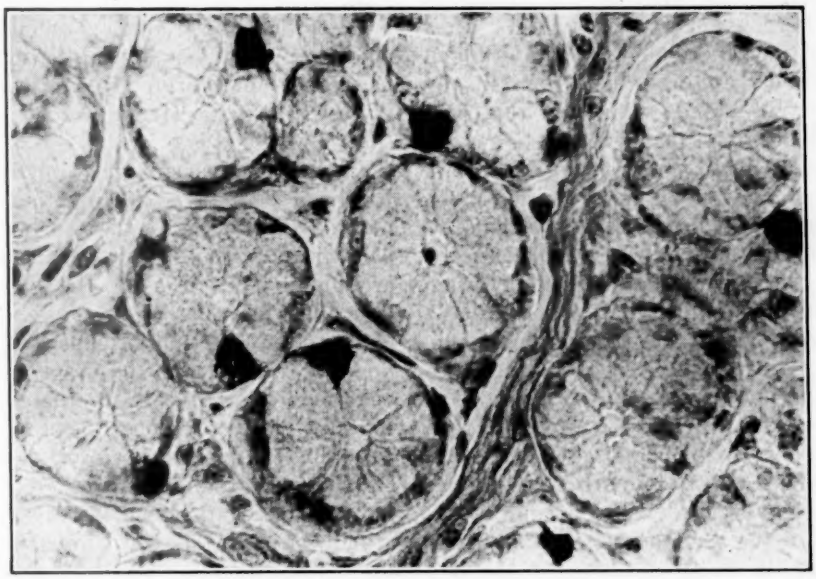

FIG. 4.—Cross section through pyloric glands of the hog. Section with fairly numerous argentaffin cells. Triangular shape of granulation, dense, most often concealing the nucleus.

FIG. 5.—Longitudinal section through fundic glands of the hog, showing scattered big, argentaffin cells of polyhedral shape.

rather large, reminding one of the duodenal cells. They are not so numerous here as in the duodenum. Most often they are triangular as if wedged in between the other cells, forced away from the lumen, with their base toward the basal membrane. The granulation is dense, most often concealing the nucleus. In the fundus (Fig. 5) the occurrence of these cells is more scattered, but they are seen in every section examined. They are rather large, polyhedral, on the whole more variable in form than those found in the pylorus. The granlation is dense, often concealing the nucleus.

Discussion. In the duodenum (in man as well as in the hog) the argentaffin cells are found to be particularly abundant and well developed and essentially of the same appearance as in the rest of the small intestine. In the hog the pylorus and fundus also show well-developed argentaffin cells though more scattered. They are relatively less numerous in the fundus. It has not been possible here to confirm the statement made by Jacobson: ". . . that the argentaffin cells are practically absent in the fundus". In our specimens these cells are seen constantly, being more scattered than in the pylorus but present in every section.

The pyloric and fundic argentaffin elements in man, on the other hand, show no morphological resemblance to the intestinal ones or to the cells in the hog, and the elements found are inconspicuous. An exception is the occurrence of large, plump, argentaffin cells in intestinal ectopies in the pyloric mucosa. In these ectopic islands are found argentaffin cells of the intestinal type, often in a considerable number. But, like the surrounding intestinal cells, they cannot be reckoned as true pyloric elements. It is the prevailing view that the ectopic islands in the stomach (apart from the scanty occurrence of congenital islands of this kind) signify pathological processes of regeneration in the mucous membrane, a feature in the histological picture encountered in chronic gastritis (cf. Hamperl[13b] and Henke and Lubarsch[14]).

In his brief histological statement Jacobson[15a] does not mention the marked differences in the morphological aspects of the gastric and intestinal argentaffin cells in man, the morphological differences of the argentaffin cells in the stomach of man and the hog, the difference in the degree of development of the cells in these locations, or the occurrence of ectopic argentaffin cells in the pylorus of man. On the background of these great differences it would seem irrelevant to attempt a more detailed comparison of the distribution.

The present studies on the argentaffin cells in man on the whole confirm the findings reported by Hamperl, by Gillman, and by Gomori.

The results obtained so far as to the localization of the hemopoietic active principle in the fundus, pylorus, and duodenum in man and the hog are obtained by testing in patients with untreated pernicious anemia the blood-forming activity of preparations made from the desiccated and defatted fundus, pylorus, and duodenum of man and the hog and by administration of pure secretions (pouch secretions) from the pylorus and duodenum of the hog. In contrast to the assumption advanced by Jacobson, it is evident that the conditions in man and the hog are not identical (Tables 1 and 2). As far as the fundus is concerned the difference is conspicuous. While preparations made from the human fundus have proved very active[9,21a,b], it has not hitherto been practicable to make from the hog fundus any preparation with antipernicious effect[9,25a,b,d,33].

If, in spite of the marked difference in the cellular morphology, we try to correlate the argentaffinity with the occurrence of the hemopoietic active principle (Table 2), it is evident that preparations from the human fundus are highly active in spite of a minimal occurrence of inconspicuous argentaffin elements, and that preparations from the hog fundus are inactive in spite of a degree of development of the argentaffin elements which at any rate is higher here than in man. The pronounced antipernicious-anemia effect of preparations from the human fundus is quite in keeping with the localization of the pathologic-anatomical changes in the gastric mucosa in pernicious anemia, that is, chiefly in the fundus[6,24,25e,35]. The ineffectiveness of preparations from the hog fundus is a striking observation. Here, particular circumstances appear to assert themselves. It is obvious, however, that there is no parallelism between antipernicious activity and argentaffinity, as such parallelism among other things would require a particular development of the argentaffin cells in the human fundus, and the opposite is found to be the case. It may be added that preparations from the human duodenum appear to be only slightly active[19] in spite of the maximal argentaffinity encountered here, and that preparations from the human jejunum, with well-developed argentaffin cells, have shown no antipernicious activity[19]. The circumstance that well-developed argentaffin cells on the whole appear to occur in the human stomach only in ectopic islands of intestinal mucosa as seen in chronic gastritis does not suggest that these cells constitute the site of the elaboration of the hemopoietic active principle (Castle's intrinsic factor) of the human stomach.

TABLE 2.—OCCURRENCE OF THE HEMOPOIETIC ACTIVITY AND ARGENTAFFINITY IN FUNDUS, PYLORUS, AND DUODENUM OF MAN AND THE HOG

	Occurrence of Hemopoietic Activity		*Argentaffinity*	
	Man	*Hog*	*Man*	*Hog*
Fundus	++	−	(+)	+
Pylorus	+	++	(+)	+
Duodenum	+	++	++	++

Conclusions. 1. The Masson silver technique reveals a marked difference in the morphology and the degree of development of the gastric argentaffin cells in man and in the hog.

2. Apart from the argentaffin cells occurring in intestinal ectopies in the human stomach, the gastric argentaffin cells in man are inconspicuous and show morphologically no similarity to those found in the intestinal mucosa or to those in the hog stomach and intestine.

3. Clinicotherapeutic investigations have shown a marked anti-pernicious anemia effect of the desiccated and defatted human fundus while all attempts to demonstrate any effect of the hog fundus have failed.

4. The pronounced effect of the human fundus is not associated with any marked argentaffinity in this portion of the stomach.

5. In view of these observations it does not seem justifiable to assume that a striking parallelism in the distribution of the argentaffin cells and the localization of the principle active against pernicious anemia lends support to the assumption of the significance of these cells to hematopoiesis.

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N-ALLYL-NORMORPHINE IN THE TREATMENT OF MORPHINE OR DEMEROL NARCOSIS*

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Severe opiate poisoning apparently is not seen often in this country, but moderate overdosage is encountered frequently, due either to untoward reactions to average doses of opiate or to errors in calculation with the subsequent administration of overdoses of the drugs. Treatment of the resulting depressions usually has been symptomatic, with only cautious resort to analeptic agents. The efficacy of the latter drugs in treating opiate narcosis has been variously described[3,12]. Picrotoxin is said to be contraindicated[6,7]. No specific antidote for opiate poisoning has been reported, but the availability of such a drug would be invaluable. The results of an investigation of the action of n-allyl-normorphine in counteracting morphine or demerol depression reported herein suggest that this drug may be a specific opiate antidote.

Experimental Background. In 1941 McCawley, Hart, and Marsh[8] first prepared n-allyl-normorphine and mentioned that the drug antagonized the depression of respiration evoked by morphine sulfate. The first data were those of Unna[13], who observed in 1943 that the drug would antagonize the depressant effects of morphine in mice if given subsequent to the injection of the opiate, and would prevent morphine from being effective if given prior to the drug. These data were verified later by Hart and McCawley[4].

The only work published since 1944 has been in the form of abstracts which have reported the following: In dogs anesthetized with barbiturates, n-allyl-normorphine was effective in preventing the respiratory depression produced by codeine, dilaudid, metapon, and methadon as well as by morphine, but was ineffective against that produced by demerol[5]; the analgetic activity of n-allyl-normorphine in dogs and rats was definite but weak[11]; the subcutaneous injection of 30 to 75 mg. of n-allyl-normorphine in post-opiate addicts produced lethargy, mild drowsiness, vivid daydreams, dysphoria, and mild cardiorespiratory depression[14]; n-allyl-normorphine was a slightly more potent inhibitor of cholinesterase than was morphine[1].

Methods. Suitable patients scheduled for minor operations received morphine (8 patients), demerol (5 patients) or morphine and demerol (2 patients). A nitrous oxide–oxygen anesthesia was then administered for the operation and additional doses of the

* This investigation was supported (in part) by a research grant from The National Heart Institute of the National Institutes of Health, Public Health Service.

opiates were administered intravenously. The largest total dose of morphine was 90 mg. and of demerol 600 mg. within a 2-hour period or less. The effect of n-allyl-normorphine was also tested in patients who had received other primary anesthetic agents: pentothal (2 patients), cyclopropane (2 patients), ethyl ether (3 patients). Following completion of the surgical procedure, the patients were transferred to a post-anesthetic observation room where respiratory minute volume and rate were measured by means of a small spirometer, and blood pressure was recorded by an intra-arterial Lilly capacitance manometer[9] (13 of 27 patients or subjects) or by ordinary auscultatory methods. N-allyl-normorphine* was administered rapidly intravenously in 5 or 10-mg. doses with a maximum total dose of 30 mg.

The procedure in 5 normal control volunteers was somewhat different. Each was placed on a tilt table and continuous recording of blood pressure begun. After a suitable period of rest the subject was tilted head up at 60° for 15 minutes and then returned to the supine position. Respiratory rate and minute volume were measured for 5 to 20 minutes. Five or 10 mg. of n-allyl-normorphine were then injected rapidly into the tubing of a previously inserted intravenous infusion of 5% glucose in water. After 15 minutes of observation, the subject was again tilted for 15 minutes. Following return to the supine position the procedure was terminated. One volunteer of 6 did not receive an injection of n-allyl-normorphine, because he fainted during the control tilt.

To determine whether or not n-allyl-normorphine could inhibit the narcotic effect of opiates, 10 or 15 mg. of normorphine were injected intramuscularly in 4 patients scheduled for minor operations under regional anesthesia. Thirty minutes later, 30 mg. of morphine sulfate were injected intramuscularly or intravenously. Respiratory minute volume was not recorded, but pulse, blood pressure, and respiratory rate were observed as were the sedative and narcotic effects.

Results. 1. MORPHINE. As indicated in Fig. 1 and Table 1, n-allyl-normorphine effected a dramatic response in counteracting the respiratory depression produced by morphine. The respiratory rate was consistently doubled or tripled in all patients following the intravenous injection of 5 or 10 mg. of n-allyl-normorphine, and respiratory minute volume was increased up to 250%. The stimulating effect on minute volume was not sustained; it reached a peak within 1 to 2 minutes, began to taper off, yet remained definitely above the depressed level for the period of observation. Respiratory rate, however, remained at or close to the peak rate. In these investigations, second injections of n-allyl-normorphine were less effective than the first and third injections were ineffective.

N-allyl-normorphine slowed the heart rate. This was contrary to the observation in animals where tachycardia was the rule. If blood pressure in the narcotized patient was within normal limits, normorphine had no marked or consistent effect, but where the blood pressure had been depressed by the opiate, the antagonist uniformly caused a rise in pressure (Table 1). The increase in blood pressure was not sustained at the peak rise, but declined to a lower level, which was always above the depression level. The circulatory effect was slower in onset than the respiratory response, usually taking 5 to 10 minutes to reach a maximum.

There was evidence of some awakening produced by n-allyl-normorphine, but it was not remarkable and could in no way be compared with that produced by metrazol or nikethamide in antagonizing mild barbiturate narcosis. The objective analeptic response was delayed 10 to 20 minutes, but in no instance did the patient awaken. The result was an apparent lightening of the narcosis so that the patient would respond to stimulation or questioning, but when undisturbed would go back to sleep. An example was the patient who received 90 mg. of morphine sulfate and subsequently was

* Supplied through the courtesy of Merck and Co., Inc.

given 20 mg. of n-allyl-normorphine. The observations were concluded when the patient would not tolerate the face-piece of the spirometer, yet she was returned to the ward to sleep for 16 hours without evidence of depressed respiration.

In the 4 patients to whom 10 or 15 mg. of n-allyl-normorphine were given intramuscularly, 30 mg. of morphine sulfate administered intramuscularly or intravenously 30 minutes later produced no significant respiratory or circulatory changes. Respiratory rate did not fall below 18 per minute in 3 patients and in the fourth the change was from 14 to 12 per minute. The sedative action of morphine was evident, to a lessened degree, however.

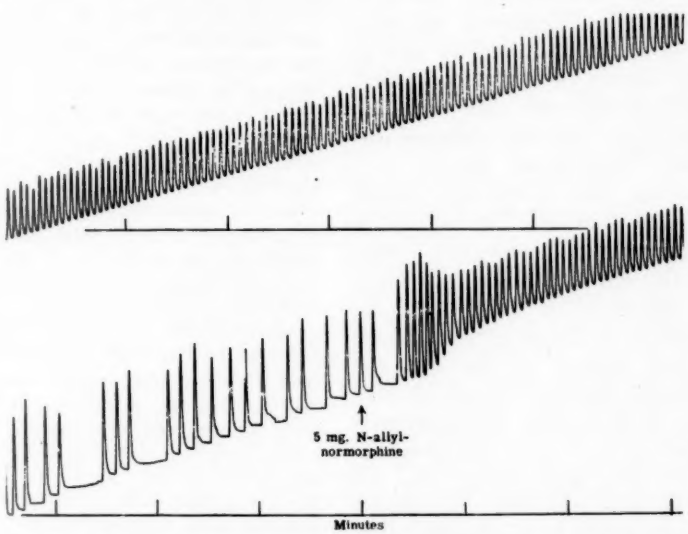

FIG. 1. Effect of n-allyl-normorphine on respiratory depression caused by 57 mg. morphine.

TABLE 1.—EFFECT OF N-ALLYL-NORMORPHINE ON RESPIRATION AND CIRCULATION DEPRESSED BY MORPHINE

J. H. Age: 24 Wt.: 120 lbs. Ht.: 5'3" White female
3/16/51 M.S. 57 mg. over 1 hr. 50 min. period. B.P. 105/60

	Resp. Rate	*Min. Vol.*	*Pulse Rate*	*B.P.*
Control 2 min.	6	3800		
1 min.	5	2920	56	68/44
N-allyl-normorphine 5 mg. I.V.				
			1 min. 60	72/45
2 min.	15	6030	3 min. 56	90/58
5 min.	16	5800	54	93/62
10 min.	15	5120	54	101/68
22 min.	13	4700	51	106/72
N-allyl-normorphine 5 mg. I.V.				
			1 min. 51	108/73
2 min.	15	5130	3 min. 50	121/74
5 min.	16	5150	51	117/76
10 min.	16	5150	2	114/74

2. DEMEROL. N - allyl - normorphine was effective in combating the respiratory and circulatory depression produced by demerol in total dosage up to 600 mg.

3. ANESTHETIC AGENTS. N-allyl-normorphine was ineffective in combating depression produced by pentothal, cyclopropane, or ethyl ether.

4. VOLUNTEER CONTROLS. N-allyl-normorphine was administered intravenously to 2 normal volunteer males in 5-mg. doses and to 3 others in 10-mg. doses. The effects of both doses were comparable. Respiratory rate was only slightly changed and that change was inconsistent. Respiratory minute volume, however, was uniformly diminished an average of 35%. The maximum diminution occurred in less than 5 minutes, and the effect persisted for more than 35 minutes. In 3 subjects no marked action on heart rate or blood pressure was noted; in the 4th the blood pressure gradually declined from 125/75 to 75/40 during the 15-minute observation period, and fainting occurred 8 minutes after tilting. The 5th subject, who had shown no circulatory abnormalities while in the supine position, fainted 10 minutes after tilting. One fainter had received 5 mg. of n-allyl-normorphine and the other 10 mg. All controls commented upon a feeling of tiredness following injection of the drug; one went to sleep during the 15-minute observation period. None noted nausea. All developed a pallor similar to that often noted after normal individuals are given morphine intravenously.

Therapeutic Use. Case Reports. PATIENT 1. M. L., white, a male, age 75 years, had arteriosclerotic heart disease, coronary insufficiency, auricular fibrillation, and mild congestive heart failure. He was orthopneic, with Cheyne–Stokes respiration, and had frequent attacks of severe anginal pain requiring nitroglycerine for relief. At 11:30 a.m., 5 mg. of morphine sulfate were ordered for restlessness. By mistake 50 mg. were administered intramuscularly. At 4:30 p.m. the patient was increasingly restless, apprehensive, and moderately cyanotic. The mistake was discovered at this time. At 5:00 p.m., if undisturbed, the patient would go to sleep and then cease to breathe. It was necessary for someone to keep reminding him to breathe. These voluntary respirations, however, were shallow. A persistent cyanotic suffusion was present across the neck and chest. The fingernails and lips were blue. Pin-point pupils were not present, because homatropine had been instilled into the eyes (at 1:00 p.m.) to facilitate ophthalmoscopic examination. Diaphoresis was profuse. The blood pressure was 116/76 and the pulse rate 92. At 5:17 p.m., 10 mg. of n-allyl-normorphine were administered intravenously. In 35 seconds an intense respiratory stimulation occurred with rapid, deep respirations. In 2 minutes the patient complained of severe anginal pain which required 2 sublingual nitroglycerine tablets for relief. Following this attack, the blood pressure was unchanged from that prior to the injection of n-allyl-normorphine, but the pulse rate increased to 108. Cheyne–Stokes respirations reoccurred with periods of apnea up to 40 seconds. However, the cyanosis disappeared, the skin became dry, and the apprehension lessened. The periods of apnea decreased in duration, and by 6:00 p.m. the breathing was regular. There was no regression thereafter. He succumbed suddenly 5 days later from a massive, acute cerebral hemorrhage.

PATIENT 2. H. C. E., white, a male, age 5½ weeks, weight 6 pounds and 11 ounces, had hypertrophic pyloric stenosis. The patient was a lethargic and malnourished infant scheduled for a Ramstedt operation. Preanesthetic medication consisted of morphine sulfate (gr. 1/480) and scopolamine (gr. 1/600) subcutaneously at 7:00 a.m. The infant was quite depressed when brought to the operating room at 7:30 a.m. Nitrous oxide, cyclopropane, oxygen, and ether endotracheal anesthesia were administered without incident. One hour postoperatively, the baby was still depressed, had little muscle tone, and respirations were 22 per minute and noisy, due to soft tissue relaxation. There was no odor of anesthetic on the breath. In view of the preanesthetic depression, the consensus was that the patient had received an overdose of morphine. Either morphine (gr. 1/480) had been too much for such a malnourished infant or a mistake in preparing the drug had been made. N-allyl-normorphine, 0.1 mg., was

administered intravenously. There was no marked respiratory stimulation, but within 2 minutes the muscle tone had improved remarkably, the respiration became quiet and slightly deeper, and the child moved spontaneously. Blood pressure and pulse remained unchanged. In 10 minutes, the child cried if disturbed. He was returned to the ward in 30 minutes in good condition.

Discussion. N-allyl-normorphine is a most interesting drug. Administered to a normal individual, it acts as a depressant to respiration and circulation; injected into man prior to the administration of a large dose of morphine, it inhibits the respiratory and circulatory depressant actions of the opiate; injected into a patient narcotized from large doses of morphine or demerol, it causes a strong respiratory and circulatory stimulation. In spite of these stimulatory actions, n - allyl - normorphine seems to do little to counteract the sedation produced by opiates, and it does not affect depression produced by other drugs.

In these studies, the effectiveness of n-allyl-normorphine in stimulating the respiration of heavily narcotized patients was dramatic. The deep, slow respirations characteristic of opiate poisoning suddenly disappeared in 15 to 20 seconds after injection of the antagonist, to be replaced with regular but less deep breathing, approximately 3 times faster. While the increased minute volume was not sustained at its maximum, the increase that was maintained was of sufficient degree to be of clinical importance. It is of interest that change in the character of respiration was not a gradual one, such as that seen with picrotoxin; nor was there an intense stimulation, followed by a gradual decline in rate and minute volume, as seen with metrazol or nikethamide.

The effect of n-allyl-normorphine on the circulation of the narcotized patient was not as consistent or dramatic as the respiratory effect. In these investigations, where blood pressure was depressed, the antagonist caused a return toward the levels normal for that patient. Where blood pressure was within the normal range for that patient, there was no marked change. The pulse rate uniformly slowed in any event.

We have no ready explanation why normorphine stimulated respiration and circulation, yet accomplished little toward awakening the patient. This is different from the other analeptic agents, which seem to stimulate all modalities equally. The same failure to awaken was seen in converse when normorphine was administered to patients followed later by 30 mg. of morphine intramuscularly or intravenously. The respiratory and circulatory actions were fairly well blocked, but the sedative effects were apparent, although not to the extent usually seen with 30 mg. of morphine.

In normal man there was a respiratory depressant action, particularly on minute volume, but not significantly upon rate. The effect on the circulation was not marked in 3 volunteer controls, but 2 others developed a circulatory instability, as manifested by fainting when tilted to the 60° head-up position. These effects are similar to those seen with the intravenous injection of morphine[2].

Although the effectiveness of n-allyl-normorphine has been investigated only against morphine and demerol, animal work suggests that it should be equally effective against depression produced by codeine, dilaudid, methadon, and metapon.

The site of action of this antagonist has not been defined, but it is probably central. The suggestion is apparent that it acts in a competitive fashion with the opiate for certain receptors. If given prior to the administration of the opiate, it occupies the receptor and blocks

the opiate; if injected after the opiate, it is able to displace the opiate from the receptor. The fact that normorphine neither blocks completely nor displaces completely the sedative effects of opiates suggests that this action may be of a non-specific nature. It would be of interest to determine the opiate blood levels before and after administration of normorphine.

One must speculate about the chemical makeup of n-allyl-normorphine. What is the specific structural unit in this drug that causes stimulation? It is structurally identical with morphine except for the replacement of a methyl group, yet it is effective against demerol, the formula for which is quite different. Although an attempt has been made to demonstrate a close structural relationship between all opiates[10], there is little agreement of such a relationship existing between demerol and morphine. Could there be a specific activity of the structural unit concerned in n-allyl-normorphine? Would it be possible to prepare n-allyl-northiopental or n-allyl-norcyclopropane?

Therapeutically, the drug appears to be of clinical value, particularly in treating mild or moderate depression from opiates. Stimulation to respiration and circulation would be desirable even in the absence of awakening. Anoxia and carbon dioxide accumulation, prime factors in causing death in opiate poisoning, could thus be obviated. So far as is known the sedative effects of opiates are not harmful per se. Failure to awaken the patient may have been because the initial doses we have used were too small.

The value of this antagonist in treating an overwhelming depression from opiates is an unknown factor at present, since repeated doses have had a decreasing effect and there is a suggestion that they may cause further depression. The usefulness of the drug under such conditions can only be determined by clinical trial.

N-allyl-normorphine may prove to be helpful in 2 other situations: 1) in the treatment of the circulatory collapse that is sometimes seen following the administration of morphine and demerol, particularly in elderly individuals, and 2) to stimulate an overly depressed mother and baby just prior to the delivery of the infant. This latter aspect is under investigation at present.

Summary. 1. N-allyl-normorphine was administered to patients who had received 20 to 90 mg. of morphine sulfate and 150 to 600 mg. of demerol. It produced a dramatic respiratory and circulatory stimulation, but effected little awakening.

2. Against depression produced by pentothal, cyclopropane or ethyl ether, n-allyl-normorphine was ineffective.

3. In normal volunteer controls, n-allyl-normorphine produced respiratory and circulatory depression similar to that seen following the injection of morphine.

4. The therapeutic effectiveness of the drug is presented in 2 patients who had received overdoses of morphine.

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PROGRESS REPORT ON ACUTE INTESTINAL OBSTRUCTION

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SINCE the previous report on acute intestinal obstruction by Ravdin and Johnston appeared in this journal 11 years ago[78], a clearer understanding of the pathologic physiology has been forthcoming.

The overall mortality is now generally reported from the larger clinics to be somewhere in the range of 10 to 20%[13,26,32,63,66,68,87]. Of more significance, however, is the fact that in cases of simple intestinal obstruction not complicated by compromise of the blood supply, the mortality has been reduced to around 5%[32,68]. This very appreciable reduction in mortality in simple obstruction has been a logical result of the clinical application of knowledge gained in the laboratory. There is now general agreement on the pathologic physiology of high simple intestinal obstruction. Death in these cases may be attributed to the loss of fluid and electrolytes through vomiting with a resulting dehydration[1,8,17,89].

In low simple intestinal obstruction the problem is somewhat more complex, but in the light of recent knowledge none the less similar. It has been noted by many investigators that animals having a low obstruction will die usually between 8 and 14 days[33,43,45], without decrease in blood chlorides, hemoconcentration or evidence of dehydration[33] and in spite of parenteral saline solution[33,48]. For this reason the possibility of absorption of toxic substances from the bowel lumen has never been entirely discarded[17]. However, more recent studies have indicated that the laboratory studies ordinarily taken in cases of obstruction

may not necessarily reflect the true status of the animal[2], and blood and plasma volumes have demonstrated that the reduction of plasma volume in low simple obstruction may be of such magnitude as to cause death of the animal[39]. It is true that the fluid may not be lost by vomiting in low obstruction[72], but it will be lost into the peritoneal cavity, into the gut wall[89,39] and, due to alterations in the absorptive capacity of the distended gut, into the gut lumen[72,89]. Further evidence against the absorption of any toxic material as the cause of death is afforded by other experiments in which animals have been kept alive for periods of 45 to 70 days by feeding through an enterostomy below the obstruction[49,50], by parenteral alimentation[72]; or by obviating the factor of distension[96]. It would seem, therefore, that the lethal issue in simple obstruction is related almost entirely to the ability to maintain fluid and electrolyte balance, or to the presence of associated complicating factors such as carçinoma[32,68], heart or kidney disease or related abnormalities.

The pathologic physiology of strangulation obstruction is less well understood. It has been amply demonstrated[4,34,39,48,60,61,88] that shock and electrolyte imbalance thru the local loss of fluid[34] may account for death in long loop strangulations in the experimental animal. If this were the only mechanism concerned, however, it would be reasonable to expect a reduction in the mortality with the more liberal use of blood and plasma and a clearer understanding of electrolyte replacement therapy. However, the mortality in those cases where gangrenous gut is found at operation still ranges around 20 to 40%[13,26,54,63,68,87], indicating that other factors are concerned with the lethal issue.

If a 30-cm. segment of gut is strangulated in a dog, death will result in 7 to 24 hours if the animal is untreated[34,36,48,60,65,67,94]. Intensive treatment for shock, hemorrhage and electrolyte imbalance will result in a definite though limited prolongation of survival time to around 30 to 36 hours[10,11,70]. If, in addition to the intensive supportive therapy, antibiotics are administered[10,11,14,19,85,86], there is a further definite though limited prolongation of survival time, thus indicating that bacteria or their end products play some role in the demise of the animal[67,88].

In spite of adequate supportive therapy and large amounts of the antibiotics, however, death will nevertheless occur in the experimental animal in around 72 hours, thus indicating that toxic factors, not amenable to present methods of treatment and probably originating from the gut lumen, continue to exist[10,70].

The lethal action of the contents of a strangulated loop of gut has been shown by many investigators[12,37,48,56,62,67,100] but there has been no conclusive evidence for the absorption into the blood stream of the intraluminal contents, nor can it be stated that death would result even if such substances were absorbed.

The occlusion of the veins to a segment of bowel as occurs in experimentally produced strangulation precludes this route as a source of absorption. Some investigators[48,52,67] have held that absorption takes place through the lymphatics, but there has been no prolongation of survival by obstructing the lymphatics[89,100]. The likeliest source of absorption would appear to be from the peritoneal cavity[94,96]. In practically all instances reported, however, the peritoneal fluid removed from strangulated animals has proved to be non-toxic when injected into other

animals[12,34,60,62,67, 88,92,94], thus indicating that noxious agents from the lumen had not entered the peritoneal fluid, or else that the noxious agents were not present in suffiicient amount to be lethal when injected into other animals[100].

Recent experiments have served to clarify some of these problems. In the experimental animal, it has been shown that late in the course of strangulation obstruction in dogs intensively treated for shock, hemorrhage, and electrolyte imbalance, the bowel wall becomes permeable to its intraluminal contents and this fluid passes out into the peritoneal cavity and thence into the blood stream[70]. This series of events was unequivocally established by the spectrophotometric finding of an abnormal pigment, a hemin derivative not previously reported *in vivo*, present first in the gut lumen from around 12 hours after strangulation, then in the peritoneal cavity, and finally in the blood stream. Death of the animal occurred soon after the appearance in the peritoneal cavity of the fluid containing the abnormal pigment. Injection experiments in conjunction with spectrophotometric studies have revealed this late peritoneal fluid to be quite toxic[71].

It was pointed out that in no case was there evidence, by the spectrophotometric methods employed, that the bowel wall became permeable to its intraluminal contents before 28 hours[70]. This is considerably longer than the survival time of strangulated animals in which intensive supportive therapy is not given. Since the peritoneal fluid injection experiments[12,34, 60,62,67,88,92,94] have been from animals not intensively treated, it would appear evident that intraluminal contents were not present in the early peritoneal fluid or at least not in sufficient amounts to cause death of the animal[71].

It is reasonable to conclude, therefore, that in the experimental animal at least, in which shock, hemorrhage and electrolyte imbalance may reasonably be excluded as the cause of death, that the lethal issue depends upon the absorption into the blood stream of the intraluminal contents which cross the gut wall barrier and enter the peritoneal cavity.

Clarification of the route of absorption is also afforded by these studies. Although the characteristic intraluminal contents were present as early as 12 hours, death did not occur until soon after the late fluid, characterized by the abnormal absorption spectrum, had appeared in the peritoneal cavity, and in no case could the unusual hemin pigment be demonstrated in the blood stream until after it had appeared in the peritoneal cavity. The absorption from the lymphatics of the strangulated gut would therefore appear to be negligible.

The nature of the noxious agent in the gut contents is not clear. As stated, there is a prolongation of survival of strangulated animals treated with antibiotics, indicating that bacteria or their end products are directly or indirectly related to the demise of the animal.

Attention has been focused primarily on the clostridial group of organisms following the original work of Williams[101] and has received added impetus in recent years[5,15,41,42], since their presence could explain the morbid processes occurring in strangulation obstruction by virtue of their exotoxins; namely hemolysins[74], lecithinases[57,58], leucocidans[38], fibrinolysin[80], hyaluronidase[64,83] and collagenase[59,82].

It has been shown[15,31,55,98] that the intraperitoneal autolysis of truly sterile tissue is without effect in the dog.

However, when a sublethal dose of clostridial organisms are added to a sterile autolysing loop[15], death of the animal may be obtained. *Cl. welchii* under certain conditions produces an alpha toxin which is a hemolytic agent. Lecithinase, the lethal component of the alpha toxin[58], has the ability to decompose lecithin into a phosphocholine and a diglyceride, exerting an irreversible change on the lipoprotein component of the host's tissues[5]. The intravenous injection of alpha toxin will cause the death of an animal in a short time and autopsy findings are similar to those of animals with strangulation obstruction[102]. Recent experiments[5,90] have demonstrated the presence of lecithinase in the gut lumen of over 90% of animal having strangulation obstruction and in the peritoneal cavity of 33% of the animals. It was felt[5] that the enzymatic properties of the toxin were not the sole cause of death, but the disintegration of the various cellular elements, whose integrity is dependent upon the presence of lecithin, probably played a vital part in producing the morbidity and death. However, Cohn, Gelb and Hawthorne[14] have failed to confirm the presence of lecithinase activity in either the gut contents or peritoneal fluid.

In addition to the difference in survival times between antibiotic treated and non-antibiotic treated animals having strangulation obstruction there is also a striking difference in the condition of the gangrenous segment of gut. In the non-antibiotic-treated group with an average survival time of 30 to 36 hours[10,70] the gangrenous gut wall is almost invariably thinned out with marked destruction of all coats, particularly the mucosal layer. In the antibiotic-treated group with average survival times considerably longer[10,11, 14,19,85] the gut wall is greatly thickened, due to the hemorrhage and edema, and the normal architecture is generally well preserved. It is probable that the antibiotics exert their favorable effect, at least in part, by delaying the destructive action of the organisms on the gut wall[43,76], thereby lengthening the time at which the gut becomes permeable to its intraluminal contents[46]. That the gut wall in the antibiotic-treated animal finally does become permeable to its intraluminal contents is shown, however, by the same spectrophotometric findings[14] which were obtained in untreated animals[70], the only difference being the time of its appearance in the peritoneal cavity.

The status and method of formation of the abnormal hemin derivative are not entirely clear. It is true that it has served to clarify problems relating to pathogenesis and routes of absorption, but it may have greater significance. There is evidence[71] that there is a definite relationship between the degree of toxicity and the degree of spectral abnormality. Whether the pigment responsible for the abnormal spectrum represents hemoglobin derivatives hitherto undescribed and originating from the blood pigment under the abnormal conditions in the gangrenous segment, or whether it is that of a mixture of common hemoglobin derivatives with less common ones[30,99] has not yet been determined. It is emphasized[70] that there is no evidence directly implicating the abnormal pigment or pigments with responsibility for the toxicity. At present there is little evidence that methemoglobin[41] or other relatives of hemoglobin may be toxic with the possible exception of porphyrins.

The abnormal spectrum has been found clinically in the peritoneal fluid of a patient who died with a mesenteric thrombosis[16], a condition entirely

similar to the experimental strangulation in the dog[10,70]. Changes toward the abnormal spectrum, though of considerably less magnitude, have been found in the peritoneal fluid of patients who had resection of gangrenous intestine and then went on to recovery[16].

Clinical Application of Experimental Conclusions. 1. PREVENTION OF DISTENSION AND RELIEF OF THE OBSTRUCTION. It is obvious from the foregoing that the fundamental consideration in the patient presenting intestinal obstruction is the interruption of the progression of events before the development of gangrenous gut with its attendant hazards. It is apparent[96] that if the distension factor with its sequelae of altered permeability and decreased viability can be obviated, then obstruction may be tolerated for many days, provided the patient is kept in electrolyte equilibrium, and when death does occur, it is not due to a toxic factor.

The prevention of progressive distension or release of the obstruction must be accomplished at the earliest possible time. The value of immediate suction drainage by either a short[95,97] or long tube[3,51] has been commented upon at length in the literature and has served as a most important adjunct in the treatment of obstruction. Others[84] have recommended the use of oxygen to decrease the intraluminal pressure. Obviously, operative intervention with relief of the obstructive mechanism at the earliest possible time must be done if strangulation is to be prevented. While it is true that there may not necessarily be any correlation between the duration of symptoms and the condition of the bowel wall as found at operation[54], there is a definite relationship between the duration of symptoms and the mortality[54,63,68,91].

2. PREVENTION OF SHOCK, HEMORRHAGE, DEHYDRATION, AND ELECTROLYTE IMBALANCE. As stated, the usual studies taken in a clinical case of intestinal obstruction may not necessarily reflect the true state of the organism[2,27]. In simple intestinal obstruction, although the loss of blood may not exceed 5% of the total blood volume[4], intestinal secretions are augmented[89], large amounts of fluid are passed into the gut lumen[72], failure of absorption in the distended segment occurs, and there is a consequent reduction in the effective circulating volume with its sequelae of decreased renal blood flow, nitrogen retention, and anuria[93].

The need for replacement of salt solution in the dehydrated patient is well recognized[18,44,45,75]. Recent work on the role of potassium in body fluid physiology has added greatly to the understanding of electrolyte aberrations[20,21,22,24,25]. The gastric secretions contain approximately 10 times as much potassium as does the serum and the intestinal secretions approximately twice as much[77]. Normally almost all the potassium in these secretions is absorbed back into the blood, so that the daily feces seldom contain more than 10 milliequivalents. If vomiting is severe, however, the losses of potassium may be 10 to 20 times that amount. Falconer observed that the vomitus contained 5 times the amount of potassium present in serum[35]. It may, therefore, readily be seen that potassium deficiency will occur in intestinal obstruction. This usually is not a problem in strangulation obstruction[10,70], but it becomes a severe problem in long standing obstruction with prolonged vomiting[6,7]. Depletion of potassium is characterized by a definite clinical syndrome[6,7,81] and characteristic chemical changes of hypochloremia, alkalosis, and hypopotassemia refractory to the administration

of sodium chloride but responsive to the administration of potassium chloride. The latter may be used in the form of a 0.6 or 1.14% solution, or the solution devised by Darrow[23]. Drabkin[28] has cautioned against its injudicious use.

In strangulation obstruction, Evans[34] showed that the blood pressure was well maintained until the plasma loss exceeded 28%. Gendel and Fine[39] showed that an average of 27.4% of the blood volume (or 2.4% of the body weight) and as much as 48% of the plasma volume could be lost within 4 hours; an amount sufficient in itself to cause death. For these reasons, determinations of the plasma and blood volumes, using Evans blue dye T-1824[40,53] may be indispensable. The importance of using the 3 sample technique has been emphasized[79].

Once strangulation has supervened, the need will be for whole blood. While the hematocrit of the early peritoneal fluid is usually around 4 to 6, it has been found as high as 14 to 28[69]. From these findings and those of others[10,11,70] it is evident that blood and plasma replacement has been far too inadequate.

3. Antibiotic Therapy. The beneficial effect of antibiotic therapy experimentally in the form of sulfathiazole[85], penicillin[10,70], penicillin and aureomycin[14], streptomycin[19] has been shown and its probable mode of action discussed above. The administration of the antibiotics should be carried out if there is the slightest possibility of compromise of the blood supply[10,11,54]. Doses of penicillin in the range of 1,000,000 U. daily or of aureomycin 1.5 to 2.0 gm. daily have been advocated, and while recently reported series have been too small to be statistically significant[68], there is definite evidence that these agents have been effective in reducing mortality[54].

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OPHTHALMOLOGY

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EDEMA OF THE OPTIC DISKS IN CASES OF ENCEPHALITIS

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EDEMA of the optic disks with or without hemorrhagic and exudative extravasations is often an ophthalmoscopic entity not associated with other disease processes in the eyes. It is generally recognized that this type of edema may be an expression of one of two or possibly three basically different lesions. In recent years, the terminology used to designate these lesions has been considerably clarified.

The majority of ophthalmologists and neurologists and probably the majority of all physicians recognize and accept the differentiation between "choked disks" and "optic neuritis." This is an all-important distinction. Not so many are agreed on the difference between "optic neuritis" and "retrobulbar neuritis with visible edema of the disk," and this differentiation would seem not to be of great clinical significance. Logically, the term "papilledema" might be used to designate edema of the disk of any type or from any cause. However, general usage at the present favors considering the terms "papilledema" and "choked disk" as synonymous.

To define "papilledema" or "choked disk" briefly but accurately is not easy. A simple and fairly satisfactory definition is passive edema of the optic disk without primary disturbance of function of the optic nerve. "Optic neuritis," on the other hand, may be defined as a primary disturbance of function of the optic nerve with ophthalmoscopically visible edema of the disk. The most characteristic visual defect of optic neuritis is the central or centrocecal scotoma, which indicates involvement of the axial or maculopapillar fibers of the optic nerve. In many instances, however, the entire cross section of the nerve is involved, so that complete blindness is present. It might be considered that two distinct entities exist, axial retrobulbar neuritis with edema of the disk, and transverse optic neuritis. However, in actual clinical experience, cases are observed frequently in which the loss of vision progresses from the presence of centrocecal scotomas to complete blindness and in which characteristic scotomas can be demonstrated again in the course of recovery. Since the

amount of edema, hemorrhage, and exudation visible ophthalmoscopically depends not on the nature but on the severity of the process, it is obvious that a satisfactory differential diagnosis between choked disk and optic neuritis cannot be made by ophthalmoscopic examination alone, but must take into consideration the mode of development and course of the edema and the visual status.

Though choked disks may develop as the result of several different mechanisms, they are associated most frequently with increased intracranial pressure. In the group of cases under consideration in this review, it is important to distinguish if possible between the choked disks of increased intracranial pressure and optic neuritis. Choked disks are discovered usually when the eyes are examined, not because of a primary visual complaint, but because of the complaint of headache or because of the presence of signs or symptoms of involvement of the central nervous system. In cases of recently developed choked disks, central vision and, except for enlargement of the physiologic blind spots, visual fields are normal unless there is extraneous pressure on the optic nerves or on some other part of the visual pathways by an intracranial lesion such as a neoplasm. The edema of the disks tends to increase, or at least not to recede, until the increase of intracranial pressure is relieved or until, after a period, usually rather long, secondary optic atrophy sets in. Even with rather advanced secondary optic atrophy, some swelling of the disk may still be present. In this stage, progressive loss of vision, not of localizing significance, occurs, characterized primarily by contraction of the nasal fields with later involvement of central vision. Therefore, in choked disks, as a rule, reduction of central vision is a late symptom.

In cases of acute optic neuritis, the edema of the disks is discovered usually when the eyes are examined because of the complaint of loss of vision of varying degree which may progress rapidly to complete blindness. The edema of the disks may increase for a few days, but then tends to disappear rapidly, usually within 2 to 3 weeks at the most, leaving varying grades of residual pallor of the disks. During this period, vision tends to improve also, although in some instances blindness may remain permanently. Usually, along with the onset of loss of vision, there is the complaint of pain on rotation of the eyes, and the reaction of the pupils to light is found to be abnormal. If the loss of vision is total, the pupils do not react to light. If central vision only is lost, the pupils may respond promptly to light stimulation but redilate rapidly while the eyes are still exposed to the light (the retrobulbar pupillary reaction).

If we eliminate from consideration the rather rarely encountered cases of chronic optic neuritis, it would seem then that differential diagnosis between choked disks and optic neuritis should be a simple matter. However, this is by no means always the case, and the distinction may be particularly difficult in patients with various forms of "encephalitis" or "encephalomyelitis." Many of these patients are too young or too ill to note or to complain of a minor reduction of vision, such as might be caused by a small central scotoma. Edema of the disks is observed usually in these patients in the course of a neurologic examination. The patient may be too young or too uncooperative to permit testing of reading vision and, even if a reduction of vision is detected or suspected, it is usually not possible to obtain accu-

rate visual fields until there has been considerable improvement in the patient's general condition. In children less than 10 years of age it is difficult and often impossible to demonstrate definitely the presence of a central scotoma even when it seems very probable that one is present. So, unless disturbance of vision is quite severe, it may readily be overlooked in patients with encephalitis, and thus optic neuritis may be mistakenly designated choked disk.

In patients with signs or symptoms of disease of the central nervous system, the discovery of choked disks always raises the suspicion of the presence of an intracranial neoplasm. Although reports in the literature indicate that choked disks do occur in some cases or types of encephalitis, yet there is always a certain amount of hesitancy in making the diagnosis of encephalitis in any individual patient with choking of the optic disks. In the various types of encephalitis caused presumably by virus infection, it would seem logical to expect the development of optic neuritis rather than choked disks. And since the edema of the disks seen in these diseases tends to be rather mild and evanescent rather than progressive, it seems probable that, in most instances, the edema of the optic disks represents optic neuritis. However, most of the encephalitides, especially those associated with the acute exanthematous infections, are considered to be demyelinating diseases. And in the form of demyelinating disease which comes probably most frequently to necropsy, encephalitis periaxialis diffusa (Schilder's disease), Walsh stated that "it seems established that optic neuritis, optic atrophy and papilledema occur according to the situation of the demyelinizing lesions and the presence or absence of increased intracranial pressure." Presumably the same statement might be made with regard to other types of encephalitis.

The difficulties encountered in making a differential diagnosis between choked disks and optic neuritis in patients with encephalitis are illustrated in the following cases:

Case Reports. CASE 1. A boy, aged 6½ years, was admitted to the hospital on October 5, 1950, with the history of fever, headaches, nausea, and stiff neck for 2 weeks. Examination of the nervous system revealed generalized weakness without focal signs. There was mild pleocytosis in the spinal fluid, 26 lymphocytes and 37 polymorphonuclear leukocytes per cubic millimeter. The diagnosis of encephalitis of unknown type was made. Four days after admission a mild edema of both optic disks was noted. The right disk was elevated 1 minus diopter and the left 1 plus diopter. Vision could not be tested accurately, but it seemed good for objects around the room. The ophthalmoscopic diagnosis of choked disks was made. Five days later the papilledema had increased slightly, but within 3 weeks it had receded so that only slight blurring remained at the poles of each disk. The patient was dismissed from the hospital. During his stay in the hospital, he had not complained of any disturbance in vision. However, 11 days after dismissal, he was readmitted with the complaint of loss of vision in the left eye and pain on rotation of the eye. Tested on an "E" (illiterate test) chart, vision was found to be 6/6 with the right eye and 3/60 with the left eye. The right optic disk was normal except for slight residual fullness at the poles; the left optic disk was edematous and elevated 3 diopters. Visual field studies were not entirely satisfactory because of the patient's age, but there seemed to be a central scotoma in the field of the left eye. From the general and neurologic standpoints, the boy seemed better than on his dismissal from the hospital. The diagnosis of optic neuritis was made. At the end of a month, the edema of the left disk had receded, leaving only slight residual fullness at the poles of the disk, and the vision had improved to 6/15. Three months later, the boy appeared well, the optic disks were flat and of good color, the visual fields seemed to be normal and central color vision, tested both on the tangent screen and by pseudoisochromatic charts,

was normal with each eye. Vision was 6/5 and ability to read 14/21 with the right eye, and 6/15 and ability to read 14/21 with the left eye with the addition of a plus 3 diopter lens. The left eye was more hyperopic than the right and possibly partially amblyopic.

In this case, apparently a nonspecific type of encephalitis, the findings and course of events during the second incident of edema of the optic disk seemed to establish the diagnosis of optic neuritis rather definitely. Though it is possible that the original disk edema resulted from increased intracranial pressure, it may be more logical to assume that it also represented optic neuritis which was at first mild and underwent partial resolution with a later more severe exacerbation in the left eye. It is unfortunate from the standpoint of differential diagnosis that more careful estimates of vision were not made during the first period of hospitalization.

CASE 2. A girl, aged 10 years, was admitted to the hospital on June 20, 1951. Approximately 2 months before, she had been taken ill with fever, headache, vomiting, and drowsiness. About 5 weeks before admission, she had been admitted to a hospital in another city because of rather suddenly developed weakness of the right arm and inability to speak. At that time, "bilateral choked disks 1 diopter" were discovered. Reduction of vision was mentioned, but no specific figures were given. The cerebrospinal fluid was found to contain 570 lymphocytes and 2 polymorphonuclear leukocytes per cubic millimeter, and the diagnosis of lymphocytic choriomeningitis was made. The patient was dismissed from the hospital on the 9th day but returned 12 days later with the complaint of blurred vision. "Choked disks," elevated 2 diopters, were present. The cerebrospinal fluid was under a pressure of 400 mm. of water and contained 42 cells per cubic millimeter, 88% of which were lymphocytes. Two days later, the spinal fluid pressure was 160 mm. of water, but the edema of the disks still measured 2 diopters.

On admission to the hospital in Rochester, 18 days after the specific complaint of seriously impaired vision, the vision was 1/60 with the right eye and 2/60 with the left eye. Centrocecal scotomas, dense to a 35/330 white target, were present in the visual fields. The optic disks showed pallor, graded 2 to 3 in the right and 1 to 2 in the left, with only slight marginal blurring residual to the previous edema. The cerebrospinal fluid contained 11 lymphocytes and 5 polymorphonuclear leukocytes per cubic millimeter and a total protein of 60 mg. per 100 cc. Electro-encephalographic tracings revealed a widespread cortical and subcortical disturbance which might indicate hydrocephalus of the third ventricle. Roentgenograms of the head were negative. The consultant in neurology made the presumptive diagnosis of encephalitis of indeterminate type. Two weeks later vision had improved to 3/60 and ability to read 14/178 with the right eye, and 5/60 and ability to read 14/89 with the left eye. The appearance of the optic disks had not changed. Two months later, the home ophthalmologist reported that the vision was 6/60 and Je. 3 with the right eye, and 6/15 and Je. 1 with the left eye. The child was in good health. The optic disks were pale but showed no evidence of edema.

Here again, the differential diagnosis between choked disks and optic neuritis was not clear-cut. The original diagnoses were lymphocytic choriomeningitis and choked disks. Viets and Watts and also Spero reported mild choked disks in a case of this affection. Vision and visual fields were normal in Spero's case. Apparently the occurrence of optic neuritis has not been observed in cases of lymphocytic choriomeningitis. However, it will be noted that in the present case, reduction of vision was mentioned at the time of the first examination. At the time of the second admission to the hospital, although the cerebrospinal fluid pressure was increased to an amount consistent with the diagnosis of choked disks, vision was seriously impaired. And it might be noted that the cerebrospinal fluid pressure was found to be normal 2 days later. The edema of the disk receded rapidly within about 5 weeks, and, at the time

of admission to the hospital in Rochester, the visual field defects were rather typical of optic neuritis. If the edema of the disks and the loss of vision were caused by hydrocephalus of the third ventricle as suggested by the electro-encephalograms, it would be rather unlikely that the edema of the disks would subside and the vision improve spontaneously as they did in this case.

This child developed chickenpox on the day that she returned home from the hospital. This was about 2½ months after the onset of the original illness. Optic neuritis has been reported by Berliner as a complication of the encephalomyelitis of chickenpox. Walsh reported a typical case in which sudden bilateral loss of vision, with subsequent complete recovery, occurred 2 weeks after the onset of chickenpox. The optic disks were swollen about 3 diopters. However, he mentioned another case of optic neuritis, with loss of vision and recovery after 2 months, in which the loss of vision occurred at least a week before the appearance of the eruption. He asked: "Was the same virus responsible both for the optic neuritis and the chickenpox?" Perhaps a similar question might be asked in the present case.

Optic neuritis has been reported to occur in association with the encephalomyelitis secondary to various other diseases such as measles, mumps, whooping cough, influenza, and vaccinia. In discussing acute optic neuritis, Berliner stated: "In the demyelinating diseases, when one speaks clinically of acute optic neuritis, one means acute retrobulbar neuritis that has manifested itself by edema and congestion in the papilla. Because of the immediate and usually profound loss of vision, the edema of the optic disk seen in these diseases will not be confounded with that of early papilledema due to increased intracranial pressure in which the visual disturbance comes on later and is gradual." However, another illustration of the fact that differential diagnosis is not always easy in cases of encephalitis is furnished by the report of Lazarus and Levine. A 6-year-old boy became blind 4 weeks after the onset of whooping cough. There was no light perception, and the pupils did not react to light. Bilateral choked disks were present, the right elevated 5 and the left 4 diopters. There was weakness of the right arm and leg. The cerebrospinal fluid was under increased pressure but contained only 2 lymphocytes per cubic millimeter. The authors suggested that the blindness was caused by hydrocephalus of the third ventricle with pressure on the chiasm. However, 10 weeks later vision was 20/70 with the right eye and 20/100 with the left. The edema of the disks had receded and there was residual secondary optic atrophy. This course of events suggests that the original edema of the disks may have been a manifestation of optic neuritis. Lazarus and Levine collected from the literature reports of 9 cases of edema of the optic disks associated with whooping cough. Four of these were diagnosed as papilledema, 5 as optic neuritis. In addition there were 2 cases of probable retrobulbar neuritis with normal fundi. Satisfactory recovery of vision occurred in all but 2 cases. Hemorrhages into the meninges or brain substance, which latter may account for some cases of cortical blindness, are more common in whooping cough encephalopathy than in other forms of encephalomyelitis.

Wesselhoeft made the suggestion that the virus of mumps is of low neurotropic order but probably primarily invades the central nervous system and reaches the salivary glands through

the blood stream. Therefore, encephalitis (and presumably optic neuritis) may precede, accompany, or follow the involvement of the salivary glands. Young, Gscheidel, and Swab have reported bilateral optic neuritis in cases of mumps encephalitis. Recovery was good only in Young's case. Woodward collected 15 cases of bilateral and 2 of unilateral optic nerve involvement complicating mumps. Optic neuritis was present in 23 eyes. Recovery of vision was complete in 11 eyes, incomplete in 8, and poor in 2. Two eyes remained blind. Retrobulbar neuritis was present in 3 eyes. All recovered completely. Optic atrophy was found in 6 eyes with serious loss of vision in all. Bilateral choked disks were reported in a case of mumps meningitis by Larkin. But since the patient was stuporous when seen and vision was not determined, it is possible that this was also a case of optic neuritis.

Judging from Walsh's discussion of the subject, involvement of the optic nerve has not been reported in the encephalomyelitis following German measles or smallpox. In the encephalomyelitis following vaccination for smallpox, von Herrenschwand found reported in the literature 2 cases of edema of the disks which he considered to be optic neuritis. In both there was temporary blindness. In one case, vision returned to normal in 5 weeks; in the other, there was residual optic atrophy with moderate reduction of vision. In another case, there was said to be initial ischemia of the retina with recovery in 6 weeks; and in another, bilateral optic atrophy with permanent blindness followed the primary development of intense edema of the retina. It is difficult to determine the exact nature of these latter 2 cases. In 2 fatal cases, von Herrenschwand was able to study the optic nerves microscopically. In one of these cases, there was a pure perineuritis which was confined to the dural sheaths of the nerves and which the author thought was an extension from the disease process in the meninges. In the second case, the vision could not be determined, but the disks appeared normal to ophthalmoscopic examination. However, microscopically, there was evidence of severe primary damage to the retrobulbar portion of the left optic nerve, particularly around the central vein where there were demyelinization and even destruction of some axis cylinders. The process did not extend to the lamina cribrosa, and the optic papilla was normal.

In measles encephalomyelitis, according to Walsh, papilledema attributed to increased intracranial pressure may occur as well as optic neuritis and loss of vision due to retrobulbar neuritis without visible edema of the disks. Walsh noted the difficulty of determining the visual acuity during the early stages of the encephalitis. He stated that the optic nerves may be selectively involved in measles encephalomyelitis and that, though recovery of vision is the rule, residual pallor of the disks is often observed. He reported 2 cases which he considered to be retrobulbar neuritis with practically total bilateral blindness at the onset. In each case normal vision was regained in one eye and fair vision in the other. There was residual pallor of the optic disks in each case. In another case of probable optic neuritis the field defect was rather unusual since, in addition to loss of central vision, there was bilateral inferior altitudinal anopsia.

Berliner reported sudden loss of vision in both eyes of a 6-year-old girl 8 days after the onset of measles. There was only questionable light perception, and opthalmoscopic examination

revealed edema of the optic disks measuring 1 diopter. At the end of a month, the edema of the disks had receded and residual optic atrophy was visible. Vision was with the right eye 8/200 and with the left 10/200. Visual field studies revealed milk. generalized contraction and central scotomas. In this case, it would seem that the recovery of vision was less than usual. However, it should be noted that the elapsed time before recovery of good vision in Walsh's cases was about 6 weeks in one and about 3 months in the 2 others. That in these cases of optic neuritis associated with encephalitis the vision may continue to improve for several months is demonstrated by Case 2 in this report and also by the following case.

CASE 3. A girl, aged 7 years, was referred to the Mayo Clinic with the presumptive diagnosis of "brain tumor" because of the finding of edema of both optic disks. Ten days before admission, she had noticed some loss of vision. Three days later she had become completely blind. At the time of admission to the hospital in Rochester, May 17, 1950, vision in the right eye was 4/60 and ability to read 14/141 and in the left eye, 4/60 and ability to read 14/178. Visual field studies revealed bilateral centrocecal scotomas dense centrally to 17/330 and 35/1,000 white targets. Ophthalmoscopic examination revealed edema of the optic disks with elevation of 2 diopters in the right eye and of 1 plus diopter in the left. Examination of the nervous system failed to reveal any abnormalities. Roentgenograms of the head were normal. Electro-encephalographic tracings showed a bilateral occipital delta focus, graded 1. The cerebrospinal fluid was under normal pressure and contained 2 lymphocytes per cubic millimeter and a total protein of 10 mg. per 100 cc. A diagnosis of acute optic neuritis was made. Eight days later, there was only slight residual edema at the poles of the disks; the central scotomas were dense only to a 5/1,000 white target in the right and to a 10/1,000 in the left eye. Vision with correction had improved to 6/50 and 14/35 with the right eye and 6/60 and 14/42 with the left eye. Three months later, the vision had improved still further and was, with the proper refractive correction, 6/12 and ability to read 14/14 with each eye. Ophthalmoscopic examination revealed pallor, graded 1 plus, of each optic disk. The visual fields were normal except for slight residual enlargement of the physiologic blind spots. An electro-encephalographic tracing was normal. One year later, corrected vision was 6/7 and 14/14 with the right eye and 6/10 and 14/14 with the left eye. There was mild pallor of the disks as before, and the visual fields were normal except for slight extensions of the physiologic blind spots resembling angioscotomas.

This case was of considerable interest not only because of the gradual recovery of practically normal vision in each eye but also because of the probable cause of the optic neuritis. Six days after the onset of the loss of vision, a measles rash appeared. A fading rash was visible at the time of admission to the hospital in Rochester. Although as a rule encephalomyelitis and optic neuritis develop in measles at least several days after the appearance of the rash, it would seem possible that, as in the case of mumps and chickenpox, the same virus responsible for the measles might affect the optic nerves primarily. Probably the optic neuritis in this case was caused by measles encephalomyelitis.

In a considerable number of instances of optic neuritis, the cause is not established. Therefore, knowledge of additional possible causes of optic neuritis is of interest and value, particularly if these causative diseases are of types which permit of ready and fairly accurate diagnosis. A recent article by Hubler, Bailey, Campbell, and Mathieson aroused my interest since, although the ocular fundi were normal in their own case of encephalitis, the authors mentioned the report of a case of bilateral optic neuritis in infectious mononucleosis. They stated that the clinical manifestations of infectious mononucleosis will vary according to the type of tissues pre-

dominantly involved; a serologic diagnosis should be possible in at least 70% of patients with this disease; a heterophile antibody or Paul–Bunnell agglutination test which is positive in a titer of 1:512 or more indicates infectious mononucleosis until proved otherwise; in cases with borderline titers, repeated tests at 7-day intervals for 2 or 3 weeks may show a rise in titer to significant levels, or absorption tests with guinea pig kidney may identify the antibody as that of infectious mononucleosis; in some of the serologically borderline cases, the diagnosis may be established by the presence of a characteristic hematologic picture.

Several reports of edema of the optic disks in cases of infectious mononucleosis have appeared in the literature. However, the data presented in these reports are in the main insufficient to permit of a definite diagnosis between choked disks and optic neuritis. Clemens observed "optic neuritis" in 3 of 16 patients examined during an epidemic of glandular fever, presumably infectious mononucleosis. However, at the time of Clemens' report (1907) the terms "optic neuritis" and "choked disk" were used more or less synonymously. Gsell described definite bilateral optic neuritis which developed on the 10th day of a meningitis complicating infectious mononucleosis. The cerebrospinal fluid was under a pressure of 170 mm. of water and contained 760 cells per cubic millimeter. These findings would suggest that the edema of the disks represented optic neuritis rather than choked disks. But no statement was made with reference to loss of vision, and the edema of the disks is said to have receded slowly, which leaves the diagnosis in doubt. Pietzonka reported a case of serous meningitis in glandular fever with bilateral choked disks, 1 diopter in the right eye, and 1.5 diopters in the left. Spinal fluid pressure was high in this case, 420 mm. of water. But again no mention was made as to vision, and the course of the edema of the disks was not recorded.

In Ashworth and Motto's case, bilateral papilloretinal edema of 3 diopters was present without evidences of encephalitis or meningitis. The cerebrospinal fluid was under a pressure of 125 mm. of water, with normal dynamics, and contained only 1 cell per cubic millimeter. Roentgenograms of the head were normal. The edema had subsided by the 31st hospital day. The fact that pain was present on rotation of the eyes suggests that the edema may have been a manifestation of optic neuritis. No mention is made as to the patient's vision. The visual fields were said to be normal, but this does not necessarily rule out the presence of a small or relative central scotoma. Blaustein and Caccavo reported a very similar case with bilateral papilloretinal edema of 3 diopters. The cerebrospinal fluid was under normal pressure and contained 4 lymphocytes and 2 polymorphonuclear leukocytes per cubic millimeter and a total protein of 51 mg. per 100 cc. Here again the presence of aching of the eyes on movement suggests optic neuritis. But no mention was made as to the vision or as to the duration of the edema of the disks.

In the report of their case, Piel, Thelander, and Shaw presented data which are somewhat more helpful in determining the exact nature of the edema of the optic disks. Their patient, a man aged 21 years, complained of impairment of distance and reading vision and of pain on rotation of the eyes in addition to meningeal symptoms. The cerebrospinal fluid was under normal pressure and contained 223 cells per cubic millimeter, 70% of which were mononuclear leukocytes, and a total protein of 100 mg. per 100 cc. The ocular fundi were normal at

this time. Exact vision was not recorded. On the 13th day after admission, there were definite edema of both optic disks and some constriction of the nasal field of the right eye. By the 18th day, the edema had increased to 2 plus diopters and there was some hemorrhagic extravasation along the right inferior nasal arteriole. One month later, vision was 20/20 with each eye, the visual fields were normal, and the physiologic blind spots were of normal size. Ophthalmoscopic examination revealed slight residual blurring of the upper margins of the disks and a small hemorrhage above the right disk. The authors considered this to be a case of optic neuritis. The data presented are probably not quite sufficient to permit of a definite diagnosis.

Bernstein, and also Landes, Reich, and Perlow, stated that involvement of the central nervous system may precede the characteristic lymphadenopathy and splenic enlargement of infectious mononucleosis, so that an incorrect diagnosis of toxic encephalitis or lymphocytic choriomeningitis may be made if serologic studies are not carried out. Tidy suggested that, in fact, so-called benign lymphocytic meningitis might be the cerebral form of infectious mononucleosis. If this is so, then the edema of the disks seen in infectious mononucleosis may be, as it is said to be in benign lymphocytic choriomeningitis, a manifestation of choked disks rather than of optic neuritis. A definite decision cannot be made until more complete studies appear in the reports of future cases. I do not recall seeing a case of this type personally, and in a group of 40 patients with infectious mononucleosis seen at the Mayo Clinic, whose histories I reviewed recently, there were no cases with ocular involvement.

According to Zohman and Silverman, experimental evidence suggests that infectious mononucleosis is caused by a filtrable virus which may at times acquire neurotropic properties. That this presumed virus may affect the eyes in various ways is suggested by the report of Karpe and Wising. In their patient, there was acute loss of vision in the right eye caused by a swelling, measuring 7 diopters in height, in the macular area. The vision and fundus of the left eye were normal. Three weeks later, the edema of the macular retina was somewhat less, but associated with it was a 2-diopter edema of the optic disk. Four months after the onset, the vision was normal and the fundus was normal except for residual changes in the retinal pigment epithelium in the macular region. There were no underlying atrophic changes in the choroid. The authors made the diagnosis of retinitis and papillitis allied to the cerebral involvements described in infectious mononucleosis.

Because of the tendency to spontaneous recovery in most cases of optic neuritis of all types, it has always been difficult to assess the value of any form of therapy. A recent report by Smith of 2 cases of transverse optic neuritis is of interest in this respect. Both patients were totally blind at the onset. In the first case the optic neuritis may have been caused by a virus meningo-encephalitis secondary to "fever and sore throat," since the cerebrospinal fluid was under normal pressure but contained per cubic millimeter 86 cells, all but 2 of which were lymphocytes, and a total protein of 80 mg. per 100 cc. The cause of the optic neuritis in the second case was not determined. The cerebrospinal fluid was normal. Both patients were treated with cortisone. In the first case, 1 month after the onset and after 3 weeks of cortisone, vision had returned

to 20/40 with the right eye and 20/30 with the left. Edema of the disks measuring 1 diopter was still present. Cortisone was continued for another week and, 2 months later, vision was 20/30 with the right eye and 20/25 with the left. The disks were pale but not edematous. The course of recovery in this case was about the average to be expected without specific therapy. In the second case, after 1 week of cortisone therapy and 10 days after the onset, vision was 20/40 with each eye and the ocular fundi were normal. Cortisone was continued for 5 days more and, 8 days later, approximately 3 weeks after the onset, vision was 20/25 with each eye, the fields were practically normal, and the disks were mildly pale. Recovery in this case would seem to be slightly more rapid than average. The general impression gained from this report and from the experience of others would seem to be that further detailed studies will be necessary before it can be determined whether cortisone has a specific curative effect in optic neuritis.

Summary and Comment. Although reports in the literature indicate that choking of the optic disks can develop in cases of encephalitis, yet in the presence of true choked disks, the diagnosis of encephalitis of any type must be made with caution, in the opinion of many competent observers. Thus, in discussing lethargic encephalitis, Rae stated that papilledema has been observed, but he qualified this statement by adding that a lethargic patient with papilledema is a thousand times more likely to have a brain tumor than encephalitis. Lyle stated that choked disk is "extremely rare" in lethargic encephalitis. Duke-Elder did not mention encephalitis among the causes of papilledema. Walsh stated that choked disks have been reported "but such an ophthalmoscopic finding should always raise a question regarding the validity of the diagnosis" of lethargic encephalitis. The same statement holds true for other types of encephalitis.

On the other hand, that retrobulbar and ophthalmoscopically visible optic neuritis do occur fairly frequently in lethargic and other types of encephalitis and encephalomyelitis seems quite well established. In lethargic encephalitis, according to Walsh, "Worms and Sourdille stated that choked disc, when it does occur in this disease, always develops rapidly, recedes spontaneously and is likely to be recurrent." This statement recalls the course of events in Case 1 reported here, in which optic neuritis seemed to be the correct diagnosis. Since, as has been pointed out, differential diagnosis between choked disks and optic neuritis cannot be made successfully by ophthalmoscopic examination alone and since in many patients with encephalitis age or illness precludes satisfactory studies of vision, it would seem logical to assume that any edema of the disk seen in a patient with encephalitis should be considered to be optic neuritis until such a diagnosis can be definitely disproved.

Assuming that the cerebral complications of infectious mononucleosis are allied to benign lymphocytic choriomeningitis, it is possible that the edema of the disks seen in these cases may be caused by an increase in the volume of the cerebrospinal fluid and may therefore represent true choked disks. It should be noted, however, that as a rule choking of the disks of any appreciable height does not develop in cases of meningitis until obstruction occurs to the outflow of the cerebrospinal fluid from the ventricular system. In such event, unless drainage is established, the choking of the disks usually does not recede rapidly but tends to become chronic and to lead to permanent loss of vision.

through secondary optic atrophy or as the result of pressure on the chiasm or optic nerves by a dilated third ventricle. This course of events has not been reported to my knowledge in cases of infectious mononucleosis or benign lymphocytic choriomeningitis. The studies of vision and visual fields in cases of infectious mononucleosis with meningo-encephalitis have not been sufficiently detailed to permit of a satisfactory differential diagnosis between choked disks and optic neuritis. Spero did state that the vision and fields were normal in his case of lymphocytic meningitis with edema of the disks, and he specifically mentioned the absence of central scotomas. It is to be hoped that further carefully studied cases will be reported so that it can be determined if infectious mononucleosis can be responsible for the development of choked disks or of optic neuritis or both. Since it appears that optic neuritis may be the outstanding or sole evidence of involvement of the nervous system in cases of encephalitis or meningo-encephalitis, checking the heterophile antibody titer and the differential leukocyte counts in cases of optic neuritis of otherwise unproved origin may aid in the solution of this problem.

Too much emphasis cannot be placed on the importance of making adequate estimations of the vision and visual fields of all patients in whom edema of the optic disks is present. The studies should be as accurate and detailed as the age or physical condition of the patient will permit. Only in this way can a correct ophthalmologic diagnosis be arrived at. The differentiation between choked disks and optic neuritis may be of considerable importance in evaluating the nature and course of the systemic disease. It is essential for the prognosis of the future vision of the patient.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF DECEMBER 18, 1951

Effect of Histamine and Antihistamines on the Liberation of Certain "Shock Substances". J. L. AMBRUS, M. D., and C. M. AMBRUS, M.D. (La-Wall Mem. Lab. of Pharmacol. and Biochem., Phila. Coll. of Phar. and Sci.). Histamine injected into rabbits or guinea pigs increased the potassium level of serum and red blood cells and the level of acetylcholine and adenosine derivatives in whole blood. These changes did not occur if histamine was injected after the administration of antihistamines. In the dosage used histamine caused no hemoconcentration in rabbits. Potassium levels were determined by the Kramer-Tschidal-Fisher method, acetylcholine levels by the Chang and Gaddum method; adenosine fractions were prepared by the Barsoum and Gaddum method.

Antihistamines did not exert any therapeutic effect in Noble–Collip, hemorrhagic, or tourniquet shock, or in standard scalding, freezing, and muscle trauma. On the basis of the above data the possible role of "shock substances" in different types of shock is briefly discussed.

The Mechanism of the Toxic Action of Acrylonitrile. FREDRIC RIEDERS, Ph.D., and HEINRICH BRIEGER, M.D., D.P.H. (Dept. of Pharmacol. and Div. of Indust. Med., Jefferson Med. Coll. Phila.). Rats, dogs, and Rhesus monkeys were exposed to acrylonitrile for 7 hours in a dynamic chamber. Vapor concentrations of 25, 50, 75, and 100 parts per million were used; they were measured exactly as follows. The vapors from a measured volume of air were absorbed into distilled water. The optical density of the resulting solutions was determined at 210 millimicrons with a Beckman Spectrophotometer by balancing the instrument with the selector at .1, the transmission at 100%, and the solvent (water) in the path of the light beam.

The lowest concentrations causing gross effects were 100 ppm (parts per million) for rats and 75 ppm for dogs and monkeys. Neuromuscular, gastrointestinal, and respiratory disorders indicated anoxia, which was further evidenced by the histologic picture of the brains. Rats at 100 ppm and dogs and monkeys down to 75 ppm showed extensive degeneration of neurons, vascular budding, and gliosis. Similar changes were in evidence focally at concentrations (75 ppm for rats, 50 ppm for dogs) which did not give rise to gross toxic signs.

Venous hyperoxygenation, established by blood gas studies, occurred early; this indicated anoxia of the histotoxic type. The cause of histotoxic anoxia was established by findings of toxic amounts of HCN by the method of Gettler and Goldbaum (Anal. Chem. 19, 270, 1947) and by spectrophotometric demonstration of cyanmethemoglobin. Toxic amounts of HCN were also found in the dogs exposed to 50 ppm; they had not shown toxic signs *in vivo* but presented degenerative changes of the brain.

An index as to the relative ability of the 3 species to detoxify the HCN formed from acrylonitrile *in vivo* was obtained by determining the increase in

thiocyanate in the blood of the animals in the course of exposure.

The Decreased Clot-Accelerating Effect of Ingested Fat When Combined with Sugar. JEROME M. WALDRON, M.D., BARKLEY BEIDELMAN, M.D., and GARFIELD G. DUNCAN, M.D. (Dept. of Physiol., Jefferson Med. Coll., and Div. of Med., Pennsylvania Hosp., Phila.). Previous studies have demonstrated that the oral ingestion of fat in the form of olive oil, refined corn oil, and cream from cow's milk increases the coagulability of whole blood. This hypercoagulability is detectable within ½ hour after feeding the fat and in 1 hour a maximum decrease is attained. Over a 3-hour observation period the coagulation time returns toward normal. It has been suggested that the clot-accelerating effect of orally ingested cream may, in part, account for the beneficial effects of cream in gastrointestinal bleeding. For various reasons the effect of combining sugar with fat was studied.

Three groups were studied. One group consisted of 17 persons who were fed 60 cc. of cream one day and 60 cc. of cream plus 7 gm. of sucrose on another day. The second group of 21 received 60 cc. of cream and 60 cc. of cream plus 7 gm. of lactose on alternate days. Twenty-three persons comprising the third group received 60 cc. of refined corn oil and 60 cc. of refined olive oil plus 7 gm. of sucrose on different days. All studies were performed in pairs with a day between studies and with a reversal of the order of feeding each paired food. Both cream and refined corn oil produced a definite change in coagulation time throughout the 3-hour observation period. Although cream plus either sucrose or lactose also produced significant changes, the latter were less than when cream alone was fed and the coagulation time had returned to normal by the third hour. Corn oil plus sucrose gave similar results except that the hypercoagulability persisted through the third hour. The inhibition of the clot-accelerating property of orally ingested fat by the addition of sugar is not due to any anticoagulant effect of the sugars studied. When sucrose or lactose alone were fed, a decreased coagulation time resulted.

Circulatory Studies by Angiocardiography with Special Reference to Mitral Stenosis. HARRY F. ZINSSER, M.D., P. W. EYLER, M.D., and D. P. MCCALLIE, M.D., (Robinette Found. and Dept. of Radiol., Hosp. Univ. of Penna., Phila.). Past circulatory studies by angiocardiography have been concerned chiefly with detection of anatomic abnormalities including vascular shunts. Angiocardiography should also furnish physiologic data provided methods could be devised for quantitating observations.

For preliminary quantitation, serial changes in chamber opacity were graded independently by several of us. Opacity ratings were assigned ranging from 1 to 4 plus. With practice, independently estimated values achieved considerable uniformity, comparing favorably with more recent photoelectric measurements. When values so estimated were plotted against time, opacification curves were obtained for individual chambers and great vessels. From numerous curves, a mean opacity curve was derived.

In normal patients, mean opacity curves for right heart and pulmonary artery were similar, reaching immediate peaks by 2 seconds and fading by 6 seconds. Average left heart curves began at 5 seconds, reached peaks at 7 to 8, and faded by 10 seconds. Aortic curves occurred slightly later, but otherwise resembled left heart curves.

Right heart curves were altered in conditions such as cor pulmonale, isolated pulmonic stenosis, and Ebstein's anomaly, but not materially in mitral stenosis except where complicating pulmonary arteriolar changes were proven or suspected. Mitral stenosis, however, profoundly affected *left* heart curves. Whereas a normal left atrium could rarely be demarcated entirely from the ventricle, in pure mitral stenosis the circumference was sharply outlined for comparatively long periods. The mean left atrial curve began normally, rose to high opacity levels, and remained there for periods averaging 8 seconds, before fading at 26 seconds. The aorta and left ventricle opacified poorly and their mean curves fell within the atrial curve. Characteristic curves occurred despite normal decholin circulation times. An explanation for such findings, involving various principles of rheology, was presented.

Angiocardiography apparently has clinical value in choosing patients for commissurotomy, a) by discovering those with significant pulmonary arteriolar block, and b) by suggesting the degree of mitral valvular obstruction.

BOOK REVIEWS AND NOTICES

A Textbook of Clinical Neurology. By J. M. Nielsen, M.D. Clin. Prof., Neurol. and Psychiat., Univ. of So. Cal. 3rd ed. Pp. 709; 212 ills. New York: Paul B. Hoeber, Inc., 1951. Price, $10.00.

Dr. Nielsen's revised, reset, and partially rewritten textbook is a major contribution to a field whose leaders are attempting revitalization. Correlation of symptomatology with basic sciences, sound organization, and excellent illustrations are preserved from the previous edition. New chapters on angiography, multiple sclerosis, and epilepsy appear and emphasis throughout is placed on up-to-date available therapy. The Author's informal style and complete index should facilitate its use both as a text and reference book.

In this Reviewer's opinion it is a superior textbook for medical students and all physicians dealing with diagnosis and therapy of common neurologic disorders.

C. U.

The Normal Cerebral Angiogram. By Arthur Ecker, M.D., Ph.D., Surg. Neurol., Syracuse, N. Y. Pp. 190; 147 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $6.50.

The author writes a rather simple monograph, illustrating the technique of cerebral angiography and angiographic anatomy. The first part of the book describes the technique employed, with specific reference to apparatus, position of the patient, and the method of percutaneous puncture of the common carotid artery.

In the Reviewer's opinion, the number of cases illustrating the normal carotid and vertebral angiograms is too few. One would have to refer to the recent excellent work on the pattern of anterior cerebral artery by Ethelberg, and the recent study of approximately 500 cases of vertebral angiograms by Radnar.

The Author has stressed the importance of studying angiographic patterns of the posterior cerebral artery with reference to tentorial herniation. He believes that he can determine by angiograms the downward herniation of the temporal lobe through the incisura cerebelli or upward displacement of the cerebellum through the same structure by outlining the pattern of the posterior cerebral artery. In general, the book has practical application and will be of importance as a teaching guide to students.

H. W.

An Atlas of Normal Radiographic Anatomy. By Isadore Meschan, M.D., Prof. and Head of Dept. of Radiol., Univ. of Arkansas Sch. of Med.; with the assistance of R. M. F. Farrer-Meschan, M.D., B.S. (Melbourne, Australia). Pp. 593; 1044 ills. on 362 figs. Phila.: W. B. Saunders, 1951. Price, $15.00.

This book was written to supply the fundamentals of radiology required for any medical practice. In it the Author has attempted to fulfill some of the needs of teachers of morbid anatomy, radiology, and clinical medicine, and of general practitioners.

The student of radiology will find the work especially valuable. A sketch showing positioning of the patient and a labeled tracing accompany the radiographs. Conventional roentgen studies are covered, and in addition special studies are included. Angiocardiography, aortography, and phlebography form the basis of the chapters on the cardiovascular system.

The book is excellent for reference and a valuable addition to any medical library.

H. W.

Modern Medication of the Ear, Nose and Throat. By Noah D. Fabricant, M.D., M.S., Clin. Asst. Prof., Otolaryngol., Univ. of Illinois, Coll. of Med., Chicago. Pp. 245; 19 ills. New York: Grune & Stratton, Inc., 1951. Price, $5.75.

This book is timely and fills an urgent need. Modern Chemotherapy has greatly changed treatment in Otolaryngology and has made many formerly necessary surgical procedures obsolescent, thus increasing the importance of medical therapy. Happily this volume deals with time-tested experiencs with drugs, in addition to the recent advances.

The volume is easy to handle and read—the paper, printing and illustrations being most satisfactory. The material is well organized, practical, factual, informative and to the point, and utterly lacking in nebulous verbosity. Its list of references and indices are excellent.

The skilled hand of an expert clinician is readily demonstrated and the author's standing as a teacher is justified by this work. This book is highly recommended for the specialist and general practitioner.

C. deL.

Biological Effects of External Beta Radiation. Edited by Raymond E. Zirkle.

Univ. of Chicago, and by 7 contributing authors. New York: McGraw Hill, 1951. Price, $3.25.

This is another monograph in the National Nuclear Energy Series, prepared by The Atomic Energy Commission to make generally available much of the wartime research done as a part of the celebrated Manhattan Project.

The work reported here is part of a comprehensive program in radiobiology undertaken at that time. There is a wealth of detail on beta ray dosimetry, technique of experimental irradiation, and measurement; of total and local effects of whole body beta radiation; lethality, injury, and recovery, both in experimental animals and in human beings. At the moment, the material is not of great clinical interest, and applications of the information and methods involved are considered to be of use to only a very limited number of investigators.

R. R.

Cancer Cytology of the Uterus. By J. Ernest Ayre, M.D., Chief, Cancer Research Dept. and Director, Dade Co. Cancer Inst., Miami, Florida. Pp. 407, 362 ills. New York: Grune & Stratton, 1951. Price, $14.50.

This is an outstanding text by an investigator whose extensive laboratory and clinical experiences qualify him to report with authority on cervical cell pathology. An evaluation of the currently used methods of collecting, fixing, transporting, and staining of slides is presented. This is based upon comparative studies of each method as carried out in the author's laboratories.

Studies of cell morphology and cell behavior are correlated with histologic sections and with clinical observations in 22,000 patients. Results of these studies present convincing evidence of the reliability and importance of the concept of cervical cell pathology which the author introduces. The excellent illustrations greatly enhance the value of this volume for reference and teaching purposes.

E. C.

Diseases of the Ear, Nose, and Throat. A Textbook of Clinical and Laboratory Procedures. By Georges Portmann, M.D., Prof. of Oto-rhino-laryngology and Dean of the Sch. of Med. and Pharmacy, Univ. of Bordeaux. Translated by Fernand Montreuil, M.D., and Jules G. Waltner, M.D., College of Phys. and Surg., Columbia Univ. Pp. 713; 677 figs., 11 in color. Baltimore: Williams & Wilkins, 1951. Price, $20.

The Preface stresses the need for a book describing all procedures of clinical examination of Ear, Nose, and Throat, including thorough laboratory studies.

There are 4 chapters on each of these 3 anatomical areas: 1) Auricular Apparatus; 2) Nasal Cavities; 3) Mouth and Pharynx; 4) Larynx, Trachea, and Bronchi; 5) Esophagus. The orderly arrangement provides that the four chapters in each instance comprise: anatomy, physiology, indirect examination, direct examination.

Two chapters are offered on laboratory methods comprising: 1) Tests on the Diseased Organ; 2) Tests of a General Nature.

Those figures which are colored bear labels in French but translation is provided below each such figure.

The text embraces old true and tried procedures in diagnosis and also presents in fine style present day concepts. Therapy is not included.

The Author and Publisher present in this book a most valuable contribution to the field of Otolaryngology and the translation has been well done.

A. L.

Outline of Fundamental Pharmacology. By David Fielding Marsh. West Virginia Univ. Sch. of Med. Pp. 219; 18 figs. Springfield, Ill.; Charles C Thomas, 1951. Price, $6.00.

This is a brief, well-written introduction to the aims and principles of pharmacology. The author discusses the following subjects: Development of Modern Pharmacology; Dose-effect Relationship; Localization of Site of Action; Absorption and Distribution; Fate of Drugs; Mechanism of Action; Chemical Constitution and Biological Action; Applied Pharmacology. For additional reading, references appear at the end of each section.

This book is especially recommended for the orientation of graduate students and of laboratory workers in pharmacology and related fields. Physicians and investigators in the fields of chemistry and medical science who are not well acquainted with modern pharmacology will find much of interest in this volume.

S. E.

A Dictionary of Antibiotics. By Leonard Karel, Natl. Inst. of Health, and Elizabeth Spencer Roach. Pp. 373. New York: Columbia Univ. Press, 1951. Price, $8.50.

A dictionary of antibiotics may come as a surprise to many physicians. However, this

volume is just that and a good dictionary, indeed. It reflects the amazing developments in the field of antibiotics which with the appearance of this volume has come of age. In pharmacopoeic form is presented all of the important information which one might want to know about hundreds of antibiotics. This author is grateful to Dr. Karel and Mrs. Roach for compiling and editing so admirably the enormous volume of material on this subject.

E. S.

GROWTH AND DEVELOPMENT OF CHILDREN. By ERNEST H. WATSON, M.D., Assoc. Prof., and GEORGE H. LOWREY, M.D., Instr., Dept. Pediat. and Commun. Dis., Univ. of Mich. Med. Sch. Pp. 260; 54 ills. Chicago: Year Book Publishers, Inc., 1951. Price, $5.75.

THE Authors present in a single volume a valuable collection of data on physical and mental growth of children. The book should be of particular interest to all concerned in the field of child health since it offers in a concise, readily usable form a wealth of information on the growing child. The many charts, tables, and illustrations supplement a readable text, to which is appended a selected up-to-date list of references. Though of particular value to the child specialist, this book also is recommended to all students and workers in fields allied to pediatrics.

J. B.

FIRST ANNUAL REPORT ON STRESS, 1951. By HANS SELYE, Prof. and Dir., Institut de Médecine et de Chirurgie expérimentales, Univérsité de Montreal. Pp. 644. Montreal: Acta, Inc., 1951. Price, $10.00.

THIS book is the First Annual Report on Stress and is to be followed each year by a similar volume which is designed to present within one set of covers all pertinent work published during the preceding year. In order to have this treatise as up to date as possible, Dr. Selye has managed to include abstracts of articles which were published as late as August, 1951.

The book is divided into sections which deal not only with the general stress concept but also with the various metabolic systems. As is usual with Dr. Selye's works, this edition is extremely well documented and will, therefore, serve as a valuable source of reference for anyone interested in this field of study. The scope of the work is so great that one cannot help but wonder how it is possible to produce such an excellent and complete book each year.

It is the opinion of this Reviewer that all investigators interested in stress and its various manifestations will find it essential to have a copy of this book for constant reference.

W. P.

LEBENSERINNERUNGEN. By FRIEDRICH VON MÜLLER (edited by his daughter, HEDI KLOIBER). Pp. 260; ills. Munich: J. F. Lehmann, 1951. Price, DM $15.00.

THE eminent director of the 2nd Medical Clinic of the University of Munich has been widely accepted as the leading German internist of his day, one of the best clinical teachers, and responsible more than anyone else for having introduced modern methods of clinical study. There are not a few clinical departments in our own schools today which still adhere unnecessarily to antiquated methods that he had abandoned over 50 years ago. The present volume is an expansion by him in 1936 of the biographical essay routinely required of its members by the Leopoldina Academy of Halle, with the understanding that it would be published by his daughter, Hedi, after his death, which occurred in 1941 in his 84th year. The first 8 of the 20 chapters—about one-half of the text—carry through the pre-Munich period, illustrating a typical German 19th century upbringing, including studies in several medical schools and calls to the staff of 5 universities. Photographs, from early school days on, reveal the same over-serious countenance, characteristic of industry rather than brilliancy, that continued without change till the last decade, when a less exacting existence after retirement mellowed the cold facial expression. He was a good organizer, sincere, a direct and hard worker, who expected the same from his students and assistants. He could detect and follow desirable trends, such as clinical biochemistry in its early days, and could give a 4-hour public lecture on Special Pathology and Therapy on request. He was broad-minded in his desire to know about foreign activities (that is, outside of his Bavaria) and a good observer, but was free with adverse criticisms.

The final 2 pages about the family strike a warmer note in these recollections—perhaps in time more of Müller's compatriots will like him agree with St. Paul that "the greatest of these is love."

Doctor G. C. Robinson, who worked in Müller's clinic before the First World War, has recently expressed his admiration of Müller to me as follows: "He was a high-pressure machine. He impressed me as a very

human person, who occasionally lost his temper with stupid students, but who had in him the delightful spirit of Munich before the First World War, where the arts and sciences were combined with a joy of living that created one of the high spots of modern culture.

"Müller had a great drive for work and thoroughness, and although he did not seem to have much originality or flair for research, he had some younger men around him who were carrying on important studies."

If Germany's leadership in medical progress has been permanently lost, as now seems likely, it is good to have this published record of one of its foremost exponents.

E. K.

PSYCHOSOMATIC GYNECOLOGY, INCLUDING PROBLEMS OF OBSTETRICAL CARE. By WILLIAM S. KROGER, M.D., Asst. Clin. Prof. Obst. and Gynec., Chicago Med. Sch., and S. CHARLES FREED, M.D., Adjunct in Med., Mount Zion Hosp., San Francisco. Pp. 503. Phila.: W. B. Saunders Co., 1951. Price, $8.

ALTHOUGH most physicians admit that gynecologic symptoms can be the result of emotional stimuli, few know how to analyze and treat such problems. "Psychosomatic Gynecology" is an attempt to provide the practicing gynecologist and obstetrician with a basic knowledge of psychiatry as related to his specialty. Various obstetric and gynecologic conditions are presented and the psychogenic motivations responsible for the organic signs are discussed.

To an organically minded physician the psychodynamics involved in the production of certain gynecologic symptoms and their treatment may be difficult to accept: For instance, the Authors suggest that uterine fibroids and even ovarian cysts may be the result of a psychosexual disturbance, using as examples reports from the literature of these lesions disappearing after psychotherapy. Whether all or even most of the Authors' ideas will eventually be universally recognized remains to be seen, but in the meantime thorough study of this text will enable physicians not only to recognize emotional problems in their practices but also to solve some of them.

J. W.

HYPERTENSION. A SYMPOSIUM HELD AT THE UNIVERSITY OF MINNESOTA ON SEPTEMBER 18, 19 AND 20, 1950, IN HONOR OF ELEXIOUS T. BELL, M.D., BENJAMIN J. CLAWSON, M.D., AND GEORGE E. FAHR, M.D. Edited by E. T. BELL, M.D., Prof. Emerit., Dept. of Pathol., Univ. of Minnesota Med. Sch. Pp. 573; 125 ills. Minneapolis: Univ. of Minn. Press, 1951. Price, $7.50.

THIS excellent symposium, held in the fall of 1950 in honor of 3 illustrious men, consists of 30 papers by 24 leaders in the field of research into hypertensive and vascular disease. Published with the papers are the related questions and discussion and there are full bibliographies. Unfortunately the book is not indexed. All approaches to the hypertension problem are well covered, including pathologic anatomy, pathophysiology, psychopathology, lipids in atherosclerosis, medical and surgical management, etc. The book fills a very real need in bringing together within one volume the sum total of existing knowledge concerning the tremendously important hypertension problem.

T. D.

LOW-SODIUM DIET. A MANUAL FOR THE PATIENT. By THURMAN B. RICE, A.M., M.D., Prof. of Publ. Health, Indiana Univ. Sch. of Med., Indianapolis. Pp. 96. Phila.: Lea & Febiger, 1951. Price, $2.75.

WRITTEN by one who has had a large experience in writing for laymen and who has himself been subjected to the rigors of a low salt regimen, this volume is prepared for patients and for the wives of patients who must provide palatable low-sodium foods for their spouses. To the Reviewer's knowledge this is the best book which has become available on this subject, and is one which can be prescribed with confidence by physicians placing patients on a low-sodium regimen.

T. D.

NEW BOOKS

From a Doctor's Heart. By EUGENE F. SNYDER, M.D. Pp. 251; ills. New York: Philosophical Library, 1951. Price, $3.75.

THE author is an elderly physician who migrated from Hitler's Germany and suffered a heart attack in 1948. By the hackneyed device of answering his son's questions, the author "wishes to explain the relationship between body and soul, the nervous heart, the effect of the emotions on the heart," God and the glory of the United States. The result is a group of partly unrelated essays that are very superficial and that reveal nothing of "the inner working of his soul". This book may be of value to a type of reader unfamiliar to the reviewer. L. S.

Let's Cook it Right. By ADELLE DAVIS, M.S. Pp. 626; New York: Harcourt, Brace & Co., 1951. Price, $3.00.

Causalgia. By FRANK H. MAYFIELD, M.D., Asst. Prof. Clin. Surg., Univ. of Cincinnati. Pp. 65; 12 ills. Springfield, Ill., Charles C Thomas, 1951. Price, $2.25.

Chronology of Ophthalmic Development. An Outline Summary of the Anatomical and Functional Development of the Visual Mechanism Before and After Birth. By ARTHUR H. KEENEY, M.D., Wills Eye Hospital, Philadelphia. Amer. Lect. Ser., No. 99. Pp. 22; 3 charts. Springfield, Illinois: Charles C Thomas, 1951. Price, $2.00.

Lecciones de Clinica Medica, Diagnostico Diferencial. By LUIS GRAVANO, Adjunct Prof., Clin. Med., Facultad de Ciencias Medicas de Buenos Aires. Pp. 399; 44 ills. Buenos Aires, Argentina: Lopez & Etchegoyen, S.R.L.

Afecciones endocrinas. Mecanismo de Exteriorizacion Clinica Orientacion del Tratamiento. By EMILIO COLOMBO. Pp. 333. Buenos Aires, Argentina: Lopez & Etchegoyen, S.R.L.

A Color Atlas of Morphologic Hematology. By GENEVA A. DALAND, B.S.; edited by THOMAS HALE HAM, M.D., Assoc. Prof. of Medicine, Harvard Med. School. Pp. 74; 9 ills., 14 color plates. Cambridge, Mass.: Harvard Univ. Press, 1951. Price, $5.00.

Enzymes and Enzyme Systems. Edited by JOHN T. EDSALL. Pp. 146; 25 ills. Cambridge, Mass.; Harvard Univ. Press, 1951. Price, $2.75.

Let's Have Healthy Children. By ADELLE DAVIS, M.S., Pp. 314; ills. New York: Harcourt, Brace & Co., 1951. Price, $3.00.

Medical Clinics of North America, Mayo Clinic Number. Symposium on Diseases of the Kidney. Pp. 941-1228; 36 ills. Phila.: July, 1951. Price, $15.00 a year.

Die Narkoanalyse als initiale Methode in der Psychotherapie. By CARL FERVERS, Prof. Dr. med. et phil. Pp. 120; ills. Munich: J. F. Lehmanns Verlag, 1951. Price, DM 7.50 (paper), DM 10 (cloth).

Electron Microscopic Histology of the Heart. By BRUNO KISCH, Res. Assoc. in Cardiol., Mt. Sinai Hosp., New York, N. Y., and Joan Bardet, Res. Labs. of Inter-Chemical Corp., New York, N. Y. New York: Brooklyn Medical Press, Inc., 1951. Pp. 106; 64 ills. Price, 5.00.

Treatment of the Nephrotic Syndrome. By LEE E. FARR, M.D. Pp. 61, Springfield, Illinois, Charles C Thomas, 1951. Price, $1.75.

Deutsch-Englisches, Englisch-Deutsches Wörterbuck für Ärzte, Band I (Deutsch-Englisch). By PROF. DR. FRITZ LEJEUNE. Stuttgart: Georg Thieme Verlag. (Distributed by Grune & Stratton, New York.) Pp. 1352. Price, DM 24.

ONE of the greatest advantages of this compact German-English medical dictionary, aside from its easily read type and its convenient size, is the listing of prefixes and suffixes of Greek and Latin origin used in medical literature, with German equivalents or translations. O. F.

Food and You. By EDMUND SIGURD NASSET, Ph.D., Prof. of Physiol., Sch. of Med. and Dentist., Univ. of Rochester. Pp. 92. Springfield, Illinois: Charles C Thomas, 1951. Price, $3.00.

Planned Parenthood: A Practical Guide to Birth Control Methods. By ABRAHAM STONE, M.D., and NORMAN E. HIMES, Ph.D. Pp. 221; 26 ills. New York: Viking Press, Inc., 1951. Price, $3.75.

Psychological Dynamics of Health Education. PROCEEDINGS OF THE EASTERN STATES HEATH EDUCATION CONFERENCE, Apr. 13-14. Pp. 134. New York: Columbia Univ. Press, 1951. Price, $2.50.

Was ist, Was kann, Was nützt, Hypnose? By KARL SCHMITZ, Dr. Med. Pp. 245; 53 ills. Munich: J. F. Lehmanns Verlag, 1951. Price, DM 9.50 (paper), DM 12 (cloth).

Die Liebesfähigkeit (Kontaktpsychologie). By ERNST SPEER, Dr. med. habil. Pp. 181. Munich: J. F. Lehmanns Verlag, 1951. Price, DM 9.50 (paper), DM 12 (cloth).

Symposium on Specific Methods of Treatment. Medical Clinics of North America, Boston Number, Sept., 1951. Edited by CHESTER S. KEEFER, M.D. Pp. 1229-1576; 59 ills. Philadelphia: W. B. Saunders, 1951. Price, $15.00 a year.

Community Health Education in Action. By RAYMOND S. PATTERSON, Ph.D., and BERYL J. ROBERTS, Ed.M., M.P.H. Pp. 346; ills. St. Louis: C. V. Mosby Co., 1951. Price, $4.50.

Tobacco and the Cardiovascular System. By GRACE M. ROTH, Ph.D., Assoc. Prof. Exper. Med., Mayo Found. Amer. Lecture Series, No. 100. Pp. 66; 8 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $2.25.

Bevölkerungsdynamik und Bevölkerungsbilanz. By Prof. Dr. Friedrich Burgdörfer. Pp. 116; 29 ills. Munich: J. F. Lehmanns Verlag, 1951, Price, DM 8.

Annual Review of Biochemistry. Volume 20, 1951. Edited by J. M. Luck, Hubert S. Loring, and Gordon MacKinney. Stanford University. Pp. 648 Annual Reviews, Inc. Stanford, California, 1951. Price, $6.00

This is a review of published literature in the field of biochemistry and includes such topics as biological oxidation, enzymes, proteins and amino acids, the lipids, carbohydrate metabolism, vitamins, nutrition, antibiotics, immunochemistry, and biochemical genetics. This is a book for the serious investigator who wishes to correlate his own work with that of others and to obtain guides for future investigation. J. B.

Surgical Forum American College of Surgeons. By The Surgical Forum Committee, Owen H. Wangensteen, M.D., Chairman. Pp. 665; 260 ills. Philadelphia: W. B. Saunders Co., 1951. Price, $10.00.

This volume consists of the papers presented at the 1950 Forum on Fundamental Surgical problems constituting a part of the program at the Annual Meeting of the American College of Surgeons. In this volume papers are limited to 3,000 words and were contributed by many of the younger men in the surgical field. In them is recorded the experimental work being carried out in surgical research laboratories and clinics throughout this nation. The volume is well edited and illustrated and should be of definite interest to all surgeons and also to any physician interested in the investigative aspects of medicine. It has a definite place as a reference manual in any research laboratory. H. C.

Thyroid Function and Its Possible Role in Vascular Degeneration. By William B. Kountz, M.D., Asst. Prof. Clin. Med., Washington Univ. Sch. of Med. Amer. Lect. Ser. No. 108. Pp. 62; 10 ills. Springfield, Ill.; Charles C Thomas, 1951. Price, $2.25.

Surgical Measures in Hypertension. By Reginald H. Smithwick, M.D., Prof. of Surg. and Chair., Dept. of Surg., Boston Univ. Sch. of Med. Amer. Lect. Ser. No. 61. Pp. 95; 35 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $3.00.

Comparative Physiology of the Thyroid and Parathyroid Glands. By Walter Fleischmann, M.D., Ph.D., Vet. Adm. Hosp., Fort Howard, Md.; Instr. in Pediatr., Johns Hopkins Univ. Sch. of Med. Amer. Lect. Ser. No. 118. Pp. 78. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

Epileptic Seizure Patterns. By Wilder Penfield, C.M.G., M.D., D.Sc., F.R.C.S., F.R.S., Prof. Neurol. and Neurosurg., McGill Univ.; and Kristian Kristiansen, M.D., Asst. Surg., Oslo (Norway) City Hosp. Pp. 104; 18 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $3.00.

Clinical and Roentgenologic Evaluation of the Pelvis in Obstetrics. By Howard C. Moloy, M.D., M.Sc. Pp. 119; 68 ills. Phila.: W. B. Saunders, 1951. Price, $2.50.

A Laboratory Guide to the Anatomy of the Rabbit. By E. Horne Craigie, Ph.D., Prof. of Comp. Anat. and Neurol., Univ. of Toronto. Pp. 113; 28 ills. Phila.: Blakiston, 1951. Price, $3.25.

This book is of value to the research worker and to the pharmacologist whose studies are being made on the rabbit.

How to Sleep Without Pills. By David F. Tracy. Rev. ed. Pp. 61; ills. New York: Sterling Publ. Co., 1951. Price, $1.00.

The Effect of Hormones upon the Testis and Accessory Sex Organs. By Norris J. Heckel, A.B., M.D., Clin. Prof. of Urol., Dept. of Surg., Univ. of Ill. Coll. of Med., Amer. Lect. Ser. No. 110. Pp. 73; 21 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

Amenorrhea. By Lawrence M. Randall, M.D., Sect. on Obstet. and Gynecol., Mayo Clinic, and Thomas W. McElin, M.D., Fellow in Obstet. and Gynecol., Mayo Foundation. Amer. Lect. Ser. No. 109. Pp. 74. Springfield, Ill.: Charles C Thomas. 1951. Price, $2.25.

Hormones and Body Water. By Robert Gaunt, Ph.D., and James H. Birnie, Ph.D., Amer. Lect. Ser. No. 103. Pp. 57; 5 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

The 1951 Year Book of Medicine. Edited by Paul B. Beeson, M.D., J. B. Amberson, M.D., W. B. Castle, M.D., T. R. Harrison, M.D., and G. B. Eusterman, M.D. Pp. 696; 149 ills. Chicago: Year Book Publ., 1951. Price, $5.00.

The 1951 Year Book of Pediatrics. Edited by Henry G. Poncher, M.D., Prof. and Head Dept. of Pediat., Coll. of Med., Univ. of Ill., with collaboration of Julius B. Richmond, M.D., and Isaac A. Abt, M.D. Pp. 441; 98 ills. Chicago: Year Book Publishers, 1951. Price, $5.00.

Studies of Undernutrition, Wuppertal, 1946-1949. By MEMBERS OF DEPT. OF EXPERIMENTAL MED., Cambridge, and ASSOCIATED WORKERS. Medical Research Council, Spec. Rep. Ser. No. 275. London: His Majesty's Stationery Office, 1951. Pp. 404; ills. Price, 12s. 6d.

A Manual of Orthoptics. By JULIA E. LANCASTER, M.A., San Francisco Ophthalmic Laboratory, San Francisco, Calif. Pp. 199. Springfield, Ill.: Charles C Thomas. Price, $5.50.

711 Medical Maxims. By WILLIAM S. REVENO. Pp. 197. Springfield, Ill.: Charles C Thomas. Price, $3.75.

THE 75-page index of this book plus the grouping of the sentence-long statements under 9 headings provide a means of quick reference for both neophyte and seasoned practitioner.

The Health of Mind. By J. R. REES, M.D., Director, World Feder. for Mental Health. Pp. 207; 4 ills. New York: W. W. Norton & Co., Inc., 1951. Price, $2.75.

THE author contributes a clear, concise practical book on personality development, and the factors essential for emotional maturity. A sound discussion of psychological defense mechanisms and their relationship to psychosomatic illness should make it an excellent addition to the lending library of any physician dealing frequently with psychosomatic patients.

Introduction to Diophthalmology. By N. A. SUTTERHEIM, M.D., State Medical Qualifications, Holland. Pp. 43; 2 ills. London, H. K. Lewis & Co., 1950. Price, 7s. 6d.

STARTING with Hering's description of the horopter, and Hofmann's discussion of Hering's views, the author leads to the conclusion that the binocular perception of direction is a function of the cyclopean eye, or mid-eye reference point, while the binocular perception of depth is a function of the continuously changing convergence of the two real eyes in overcoming the horizontal disparity of the retinal images. This very short treatise is directed towards establishing a dynamic and ophthalmic concept of simultaneous binocular fixation to be called "Diophthalmology".

R. P.

Proceedings of the First Conference on Electrokymography. (May 25-26, 1950; Bethesda, Maryland; sponsored by the National Heart Institute). Public Health Service Publication No. 59. Pp. 215.

THIS booklet contains the most complete evaluation available of the possibilities and limitations of the electrokymographic method of studying heart border motion and heart and lung density changes. Most of those who have been associated with the instrumentation, physiological research, and clinical application in connection with this instrument are represented either by papers or in the discussions; the transcriptions of the latter unfortunately suffer from inadequate editing so that portions are unintelligible.

H. S.

NEW EDITIONS

Science French Course. By C. W. PAGET MOFFATT, M.A., M.B., B.Chir. Revised by JOEL CORCORAN, B.A. (Com.), B.Sc., M.Sc.Tech. 3rd. ed. Pp. 332. New York: Chemical Publishing Co., Inc., 1951. Price, $4.75.

THIS pocket-size book is divided into 5 parts. The first 2 cover grammar, Part I providing the rudiments necessary for the reading of the short descriptions of familiar objects given in Part IV and Part II providing more advanced syntax for the student who can devote the time to it. Part III groups the regular verbs into the usual 4 conjugations and classifies the irregular verbs. Part V provides readings in 9 different branches of science, with a 10th division on military studies. The physician who wants to learn enough French so that he can read journals in his specialty will find this volume helpful, whether he studied the language previously or whether he is learning it anew. The only fault of the book, if any, lies in its failure to emphasize the importance of a knowledge of idioms in order that meaningless translations of seemingly simple phrases may be avoided.

O. F.

The Infectious Diseases of Domestic Animals. By WILLIAM ARTHUR HAGAN, D.V.M., D.Sc., and DORSEY WILLIAM BRUNER, D.V.M..Ph.D., Professors of Bacteriol., State Univ. Veterinary College, Cornell Univ. 2nd ed. Pp. 920; 154 ills. Ithaca, New York: Comstock Publ. Co., Inc., 1951. Price, $8.00.

Clinical Laboratory Methods. By W. E. BRAY, B.A., M.D., Prof. of Clin. Pathol., Univ. of Virginia; Dir. of Clin. Lab., Univ. of Virginia Hospital. 4th ed. Pp. 614; 119 ills., 18 color plates. St. Louis: C. V. Mosby Co., 1951. Price, $7.25.

The Management of Fractures, Dislocations and Sprains. By JOHN ALBERT KEY, B.S., M.D., Clin. Prof., Orthoped. Surg., Washington Univ. Sch. of Med., and H. EARLE CONWELL, M.D., F.A.C.S., Assoc. Prof. Orthop. Surg., Univ. of Alabama Sch. of Med. 5th ed. Pp. 1232; 1195 ills. St. Louis: C. V. Mosby Co., 1951. Price, $16.00.

THE latest edition of this familiar book can again be considered as a comprehensive text which should be on the shelf of any physician active in fractures and traumatology. The illustrations are both copious and adequate. The handling of compound wounds and transportation of the injured is most timely. Intramedullary fixation methods are described, but in the opinion of the reviewer complications as to technical problems and/or fracture repair relevant to this method were conspicuous by their absence. In all one can readily conclude that the authors have contributed a fine text to the profession.

A. S.

Principles and Practice of Obstetrics. By J. P. GREENHILL, M.D., Attend. Obstetr. and Gynecol., the Michael Reese Hosp., Chicago;

Obstetr. and Gynecol., Assoc. Staff, Chicago Lying-in Hosp.; Attending Gynecol., Cook County Hosp.; Prof. of Gynecol., Cook County Grad. Sch. of Med. 10th ed. Pp. 1020; 1140 ills. Phila.: W. B. Saunders Co., 1951. Price, $12.00

THE 10th edition of this textbook which was originally written by J. B. DeLee has been thoroughly revised. Greenhill, the current author, has wisely called upon prominent authorities outside the field of obstetrics for certain specialized contributions. The illustrations have been improved by the substitution of many new ones and by deletion of some which have been used through several editions. The text is concise and direct and much outmoded material has been discarded. This book is equally valuable as a reference for the practicing physician and as a text for the medical student, since it includes in most instances thorough discussions of etiology, diagnosis, and treatment of the various conditions considered. J. W.

Rosenau Preventive Medicine and Hygiene. By KENNETH F. MAXCY, M.D., Dr. P.H., Prof. of Epidemiology, The Johns Hopkins University, School of Hygiene and Public Health. 7th ed. Pp. 1462; ills. New York: Appleton-Century-Crofts, Inc., 1951. Price, $14.00.

INASMUCH as 16 years have elapsed since the publication of the 6th edition of this pioneer and well-known book, the present edition prepared by Dr. Maxcy, with the assistance of 26 contributors, is greatly to be welcomed. Under the circumstances it was not only necessary to revise extensively some parts of the old book and to rewrite others, but to add some new chapters. Needless to state, this heavy revision was required not only because of the broadened aspects of environmental sanitation, but because of the increasing attention being given nowadays to the prevention of diseases of noninfectious etiology, the maintenance of health in middle and old age, and community provisions not only for the treatment and rehabilitation of the sick but of those who are physically or mentally handicapped as well. The present edition fulfills these requirements very satisfactorily. Splendidly written, along with particular attention to the selection of references to an ever increasing literature, it is a worthy successor of all previous editions of a book which many have regarded as "the Bible" in the field of preventive medicine and hygiene since it was first published 38 years ago. J. K.

Autopsy Diagnosis and Technic. By OTTO SAPHIR, M.D. Clin. Prof. of Pathol., Univ. of Ill. Coll. of Med. 3rd ed. Pp. 471; 80 ills. New York: Paul B. Hoeber, Inc., 1951. Price, $6.00.

THIS small volume, 434 pages of text and 6 pages of weights and measurements, has become over the past 15 years the standard guide for autopsy technique. As such it should be read by every resident beginning his service in Pathology and by non-pathologists who are required to perform occasional autopsies. As a text of autopsy technique it performs an admirable function. The 124 pages added since the first edition have done little, if anything, to enhance it. On the contrary, the inclusion of a smattering of pathology and pathologic physiology has complicated the text and added nothing that is not better obtained in works devoted completely to these subjects.

E. A.

The Physiology of the Newborn Infant. By CLEMENT A. SMITH, M.D., Assoc. Prof., Pediat., Boston Lying-in-Hosp., Harvard Med. Sch. 2nd ed. Pp. 365; 52 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $7.50.

SINCE the original edition of this book 6 years ago, there has been a general impetus of fundamental studies in the newborn period. The larger 2nd edition of Dr. Smith's book records this new information quite completely. Many chapters, such as fetal and neonatal aspects of respiration, circulation, renal regulation, endocrinology, immunology, and nutrition, have been rewritten.

The author's rich clinical and teaching experience combined with an unusual verbal clarity is reflected in his critical analysis of the investigative work which this book describes. Dr. Smith not only presents what is known about fetal and neonatal life but, perhaps more important, points out by direct mention or inference, the lack of information on specific subjects. Finally, all the information is integrated by a clinical summary at the end of each chapter.

This book should be standard reading for all medical students as well as for pediatric and obstetrical residents since it is a textbook of basic science for a period of life which has no physiological counterpart. The book is recommended to any general practitioner who takes care of newborn infants. The clinical summaries at the end of each chapter present practical applications of our present knowledge of newborn care, and where more information is desired than is presented in the text, an excellent bibliography is furnished. H. R.

Physical Biochemistry. By HENRY B. BULL, Ph.D., Prof. of Chem., School of Med., Northwestern Univ. 2nd ed. Pp. 355; ills. New York: John Wiley & Sons, Inc., 1951. Price, $5.75.

THE general arrangement and choice of subject matter of the 1st edition have been retained. However, much of the material has been rewritten and condensed wherever possible so that new material could be added without appreciable increase in the size of the book. The inclusion of a set of problems and questions at the end of each chapter is a valuable addition to this well-written text. This book should continue to be of great service to the student and investigator in the biological sciences who needs help in the clarification of the concepts and terminology used in physical chemistry. H. W.

Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines, and Tuberculins in Prophylaxis and Treatment. By H. J. PARISH, M.D., F.R.C.P.E., D.P.H. 2nd ed. Baltimore: Williams & Wilkins Co., 1951. Price, $2.50.

THE subtitle rather than the main title is the true reflection of the contents of this small volume

which is a practical and reliable guide to modern biologic prophylaxis and therapy. When faced with a problem concerning immunization, prophylaxis, or skin testing, the busy practitioner will find this manual the most useful available source of information. The practical detail is there in convenient form. The important topics are dealt with adequately and the unimportant ones briefly. The text is concise and lucid, the index complete. As a whole, illustrations have been carefully chosen; a few are excellent. But those of stained bacteria and of selected medical investigators are superfluous.

Unfortunately, most of the biologics mentioned carry British designations and insufficient attention is paid to its American equivalent. Similarly, references are often restricted to British publications of limited distribution in America. E. S.

Radiologic Physics. By CHARLES WEYL AND S. REID WARREN, JR., Moore Sch. of Engineering, Univ. of Penna. 2nd ed. Pp. 491; ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $10.50.

THE 2nd edition of this standard work on radiologic physics has been extensively rewritten, but the strong features of the 1st edition remain intact. Among these may be mentioned a detailed section on basic electricity, electronics, and electric measuring instruments. Almost half of the book is so occupied, and one wonders whether the first part, on electricity, does not represent an overemphasis of the subject as far as the radiologist (for whom the book is intended) is concerned.

Part 2 is devoted to radiant energy and its interaction with matter. Here the extensive revision and modernization are everywhere apparent and welcome. Paticularly well done are the discussions relating to radiation intensity and dose, and the theory of the free air and thimble ionization chambers. Radioisotope dosimetry also receives a prominent place. The reviewer regrets that Part 2 has been so compressed, by comparison with Part 1, in view of the relative availability elsewhere of the information in Part 1.

The book should receive wide favor as an intermediate text and source book on radiologic physics, bridging comprehensively the gap between the elementary texts on the subject and the specialized literature not available in a single book. R. R.

Manual of Massage and Movements. By EDITH M. PROSSER, T.M.M.G. 3rd ed. Pp. 388; copiously illustrated. Phila.: J. B. Lippincott, 1951. Price, $5.00.

THE author of this very practical, and at the same time scientific, book on massage should be well qualified for her task, having long been in charge of a Department of Massage in London and Examiner for the Chartered Society of Physiotherapy at the Middlesex Hospital since 1928. Since the first edition appeared (1938), the many thousands of war casualties have emphasized anew the importance of this form of therapy, yet it still appears to be underrated in England as well as in this country. In this Manual the opening chapter on the history of massage, though brief, and the sections on the underlying theory of the manipulations employed lift the subject well above merely detailing the maneuvers to be learned. About one-third of the text is given to this basic aspect, another third to the exercises for the several parts of the body with detailed explanations of the muscular actions involved. The numerous special terms and their abbreviations must be mastered early, otherwise those such as "Crk. ly. w. P. lift" may appear too formidable and even "crook lying" not be understandable till explained by the text.

Not only will well-equipped departments of physiotherapy want this book on their shelves; but also many physicians, as well as the masseuses at whom it is chiefly directed, will be aided by it in the management of a wide range of disorders. E. K.

Clinical Allergy. By SAMUEL J. TAUB, M.D. 2nd ed. Pp. 276. New York: Paul B. Hoeber, 1951. Price, $4.50.

Immuno-Catalysis and Related Fields of Bacteriology and Biochemistry. By M. G. SEVAG, Ph.D., Sch. of Med., Univ. of Penna. 2d ed. Pp. 524. Springfield, Ill.: Charles C Thomas, 1951. Price $12.00.

"IMMUNO-CATALYSIS" represents a noteworthy effort to organize and relate a wide range of scientific facts and theories in terms of the conception that antigens function as biocatalysts. In developing this idea the author has drawn upon the extensive literature of protein chemistry, immunology, and enzymology. Although the relevance of the material is not always clear, the stimulating view that antigens are catalytic finds much support in the many similarities of the antigenic process to other catalytic reactions. Nevertheless its adequate validation requires further evidence of its experimental productivity as well as logical clarification of the relation of the antigen to the activation energy and activated state associated with the process which the antigen is assumed to catalyse. F. K.

Tumors of the Skin, Benign and Malignant. By JOSEPH JORDAN ELLER, M.D., Director Dept. Dermatol., New York City Hosp., and WILLIAM DOUGLAS ELLER, Asst. in Dermatol., Univ. Hosp., New York-Bellevue Med. Center. 2nd ed. Pp. 697; 550 ills.; 3 plates in color. Phila.: Lea & Febiger, 1951. Price, $15.00.

THE fact that a book dealing with tumors of a single organ, the skin, has gone into a 2nd edition, indicates not only the need for such a volume, but the fact that the Ellers have produced a product which meets the demand. In spite of certain more or less minor shortcomings, this is a good exposition of the subject of tumors of the skin.

The new edition has taken into account the errors of omission and commission of the first edition. New entities have been added, although the reviewer could find nowhere a discussion of hemangiopericytoma, which has received considerable attention recently. In addition, the section on principles and technique of radiation therapy have been enlarged and brought up to date. A significant feature of the text is the stress which the authors have placed on histopathologic findings in the various tumors of the skin. The scope of the coverage in this volume is rather wide, including a comprehensive discussion of the diagnosis and treatment of the precanceroses, the

lymphomas, malignant melanoma, sarcoma, and the usual types of cutaneous epithelioma.

There is also a section on surgical procedure and plastic repair of tumors, which, however, is not intended to be the last word for the experienced practitioner of this type of therapy. The illustrations for the most part are superb, but it appears that certain of the histopathologic representations, particularly those from the Armed Forces Institute of Pathology, have a rather gray shadow on them. This, of course, could be remedied in future printing. Figures 144 and 145 could have been omitted without any serious loss to the presentation.

To one who has been interested in tumors of the skin for a long time, as has the reviewer, this volume comes as a very welcome source book.

H. B.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By CHARLES MAZER, M.D., formerly Assoc. Prof., Gynec. and Obst., and S. LEON ISRAEL, M.D., Asst. Prof., Gynec., Univ. of Penna. 3rd ed. Pp. 583; 137 ills. New York: Paul B. Hoeber, 1951. Price, $10.00.

IN this 3rd edition the Authors continue to provide "a guide to the family physician who is the first to see and treat . . . menstrual disorders and sterility." The volume describes completely the activities of each of the endocrine systems and the effects of the hormones on other organs. The disorders of menstruation and sterility are completely discussed. In the latter condition both the male and the female factors are thoroughly and clearly presented.

The great value of this volume is in its systematic and complete presentation of etiologic factors and investigation and treatment for each of the disorders considered. It is highly practical and should be a welcome addition to the library not only of the family doctor but of the gynecologist.

J. W.

Your Diabetes. A Complete Manual for Patients. By HERBERT POLLACK, M.D., Assoc. Phys. for Metabol. Dis., Mount Sinai Hospital, and MARIE V. KRAUSE, M.S., Consult. Dietician. Revised ed. Pp. 212. New York: Paul B. Hoeber, Inc., 1951. Price, $3.00.

THIS handbook for diabetic patients contains a great deal of basic physiology explained in readily understandable terms for the non-medical reader. The patient should be able to master the material as presented here without any appreciable difficulty and emerge with a much keener insight into his disease. The chapter on the history of diabetes is so interesting that one wishes it were longer. This small volume is filled with advice concerning jobs for diabetics, care of the diabetic child, and other problems intimate to many diabetic families. A complete description of the food-exchange system of diet control is included in the text.

C. S.

Untoward Reactions of Cortisone and ACTH. By VINCENT J. DERBES, M.D., F.A.C.P., Assoc. Prof. of Med., Tulane Univ. of La., and THOMAS E. WEISS, M.D., Instr. in Med., Tulane Univ. of La. Pp. 77; 1 ill. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

The 1951 Year Book of Surgery. Edited by EVARTS A. GRAHAM, M.D., Prof. Surg., Washington Univ. Sch. of Med., and STUART C. CULLEN, M.D., Prof. Surg. and Chairm. Div. Anesthes., Univ. of Iowa. Pp. 621; 209 ills. Chicago: Year Book, Inc., 1951. Price, $5.00.

Frontiers in Medicine. The March of Medicine, 1950. NEW YORK ACAD. OF MED. LECT. TO THE LAITY, No. 15. Pp. 150; 6 ills. New York: Columbia Univ. Press, 1951. Price, $2.50.

Marriage, Morals, and Medical Ethics. By FREDERICK L. GOOD, M.D., L.L.D., and REV. OTIS F. KELLY, M.D. Pp. 202. New York: P. J. Kenedy & Sons, 1951. Price, $3.50.

Physiologie des Menschen (Landois-Rosemann's). By HANS-ULRICH ROSEMANN, Prof. of Physiol., Marburg. Pp. 958; 240 ills.; 1 color plate. Munich: Urban & Schwarzenberg, 1950. Price, DM 46.60.

THIS is a splendid book in German illustrating the recovery which German science has made since the war. It is useful to the student of physiology because it is a well rounded and complete treatment of the subject.

M. O.